TUMORS of the LIVER and INTRAHEPATIC BILE DUCTS

by

JOHN R. CRAIG, M.D., Ph.D.
ROBERT L. PETERS, M.D.
and
HUGH A. EDMONDSON, M.D.

AFIP

TUMORS of the LIVER and INTRAHEPATIC BILE DUCTS

ATLAS OF TUMOR PATHOLOGY

Second Series
Fascicle 26

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ATLAS OF TUMOR PATHOLOGY

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EDITORS' NOTE

The Atlas of Tumor Pathology was originated by the Committee on Pathology of the National Academy of Sciences – National Research Council in 1947. The form of the Atlas became the brainchild of the Subcommittee on Oncology and was shepherded by a succession of editors. It was supported by a long list of agencies; many of the illustrations were made by the Medical Illustration Service of the Armed Forces Institute of Pathology; the type was set by the Government Printing Office; and the final printing was done by the Armed Forces Institute of Pathology. The American Registry of Pathology purchased the Fascicles from the Government Printing Office and sold them at cost, plus a small handling and shipping charge. Over a period of 20 years, 15,000 copies each of 40 Fascicles were produced. They provided a system of nomenclature and set standards for histologic diagnosis which received worldwide acclaim. Private contributions by almost 600 pathologists helped to finance the compilation of an index by The Williams & Wilkins Company to complete the original Atlas.

Following the preparation of the final Fascicle of the first Atlas, the National Academy of Sciences – National Research Council handed over the task of further pursuit of the project to Universities Associated for Research and Education in Pathology, Inc. Grant support for a second series was generously made available by both the National Cancer Institute and the American Cancer Society. The Armed Forces Institute of Pathology has expanded and improved its press facilities to provide for a more rapid and efficient production of the new series. A new Editor and Editorial Advisory Committee were appointed, and the solicitation and preparation of manuscripts continues.

This second series of the Atlas of Tumor Pathology is not intended as a second edition of the first Atlas and, in general, there will be variation in authorship. The basic purpose remains unchanged in providing an Atlas setting standards of diagnosis and terminology. Throughout the rest of this series, the terminology chosen for the World Health Organization's series "International Histological Classification of Tumours" will be used when available. Hematoxylin and eosin stained sections still represent the keystone of histologic diagnosis; therefore, most of the photomicrographs will be of sections stained by this technic, and only sections prepared by other technics will be specifically designated in the legends. It is hoped that in many of the new series a broader perspective of tumors may be offered by the inclusion of special stains, histochemical illustrations, electron micrographs, data on biologic behavior, and other pertinent information when indicated for a better understanding of the disease.

The format of the new series is changed in order to allow better correlation of the illustrations with the text, and a more substantial cover is provided. An index is included in each Fascicle.

It is the hope of the Editors, past and present, the Editorial Advisory Committees, past and present, and the Sponsors that these changes will be welcomed by the readers. Constructive criticisms and suggestions will always be appreciated.

William H. Hartmann, M.D.
Leslie H. Sobin, M.D.

ROBERT L. PETERS
1927 – 1985

HUGH A. EDMONDSON
1906 – 1986

Hugh A. Edmondson, professor of pathology at the University of Southern California, is remembered for his medical teaching, literary contributions, leadership in building an excellent department of pathology, and as a promoter of the university and medical school. Dr. Edmondson came to the Los Angeles County Hospital in 1932 following his graduation from Rush Medical College in Chicago. He completed a pathology residency in 1938 and became a department chairman in 1951, and later, the Director of Laboratories at the LACUSC Medical Center. In 1969, he retired from the Chairmanship and continued with his teaching, writing, and research activities. Dr. Edmondson influenced many medical students and residents for over 40 years. Many of his "usual" lectures for the second year pathology course were carefully researched in the medical library before presentation and he always provided the latest references. His histologic expertise was widely acknowledged following his postgraduate lectures. Dr. Edmondson provided insight and often references to the numerous pathology residents and practicing pathologists who came to him with difficult cases. His interest in liver disease was recognized by several classic publications in the 1950s, including the first edition of this Fascicle. Focal nodular hyperplasia and mesenchymal hamartoma were terms he introduced in that Fascicle, and as he reminisced a few years ago, he delighted in reviewing the many interesting liver tumors and completing the classification system in the Fascicle. Perhaps Dr. Edmondson's most remarkable quality was his youthful inquisitiveness. During his later years, after retiring as department chairman, he continued to read the latest journals and formulate ideas about molecular biology and the histologic evidence for the pathogenesis of numerous diseases, including alcoholic liver disease, chronic active hepatitis, and hepatocellular carcinoma. He took most pride in his publications, especially "Sclerosing Hyaline Necrosis" because he recognized that the key alcoholic hepatic lesion was centrolobular sclerosis, and that birth control pills had a role in the development of hepatocellular adenoma. "Hard writing makes easy reading" he said often as he worked on chapters in pathology textbooks. Each of his projects reflected hours of library work, review of case material, and compilation of data for tables. The university has lost a great friend. Dr. Edmondson was a tireless worker and recruiter for the school. Not only did he recruit young as well as experienced and established pathologists, but he also worked with the other departments to build the medical school.

Robert L. Peters' unexpected death in 1985 saddened many friends and coworkers around the world. Born in Redlands, California, he attended UCLA and medical school at the University of Chicago. He then returned to Los Angeles for his pathology residency. At the National Institutes of Health, he completed his residency and returned to the faculty at the University of Southern California where he was influenced by Hugh Edmondson to become the first chief pathologist at the newly formed Liver Service. Dr. Peters' broad general pathology knowledge inspired many young residents and fellows for over 25 years. His interest in medical liver disease was stimulated by the collaboration of Telfer B. Reynolds, Allen Redeker, and Hugh Edmondson, and the availability of numerous alcoholic patients and abundance of viral hepatitis from 1960 to 1985. Dr. Peters promoted the development of laboratory tests as well as special histologic technics to evaluate acute and chronic hepatitis and other hepatic disorders. During the years, fellows from around the world studied at the Liver Unit and recall the stimulation and guidance from Dr. Peters at the weekly autopsy conferences, biopsy conferences, and journal clubs. Dr. Peters took his medical school teaching responsibility seriously and devoted much time and energy to the second, third, and fourth year programs. Because of his acknowledged expertise in liver disease, few realized how talented he was in the general pathology field, but as his close associates discovered, he was interested in all areas of anatomic and clinical pathology. Dr. Peters visited many medical centers and lectured on liver disease to many state societies and international research centers.

These men devoted enormous energy and thought to this Fascicle. Many letters were written for interesting cases and many slides were culled from the consultation files for discussion. Their death precluded their completion of this Fascicle. It has been my pleasure to reflect upon my 20 year exposure to both of these men, the numerous conferences with them, and the numerous lectures we did together in order to synthesize a final version of the Fascicle. I am grateful for the support and understanding from the Editor, William H. Hartmann.

John R. Craig

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The authors wish to acknowledge the considerable assistance of numerous pathologists in supplying pathologic material utilized in the writing of the Fascicle. Most of the rare tumors were received over many years from contributors in the United States, and to a lesser extent in the Orient, Central and South America, and West Africa. In addition, Weldon K. Bullock, M.D., provided the resources of the California Tumor Tissue Registry. Tumors of infants and children accumulated at Children's Hospital Los Angeles were available through the courtesy of Benjamin Landing, M.D. and Hart Issacs, M.D. Many pathologists were kind to provide histologic material upon request and they have been acknowledged in the legends.

The secretarial assistance over many years was provided by numerous individuals in the USC Pathology Department, including Lillian Soine (Dr. Hugh Edmondson) and, in the preparation of the Fascicle, we appreciate the dedication of Emily Mader (USC Liver Pathology Unit).

The entire staff of the USC Liver Pathology Unit has been helpful, including the pathologists (Drs. Sue Govindarajan, Gary Kanel, and Chong T. Liew) and the histotechnologists (Bernard Lim, chief technologist).

John R. Craig, M.D., Ph.D.
Robert L. Peters, M.D.
Hugh A. Edmondson, M.D.

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TUMORS OF THE LIVER AND INTRAHEPATIC BILE DUCTS

INTRODUCTION

Classification of human tumors has an evolution of nomenclature and concepts that is based on the scientific efforts of many researchers utilizing many technics. The classification provided in this atlas is another revision of current concepts of the time (1983-1987) and includes some controversial categories. However, we believe that standard light microscopic examination with routine and special staining remains the standard of reference for classification. Upon review of many tumors, both old and from ancient storage files in various hospitals as well as from current files, it is clear that ideal investigation and sampling of a tumor is not often obtained. Whereas most tumors of the liver fit into "acceptable" categories, additional technics are often useful for special unusual tumors. Application of these technics in the routine tumor often produces surprising results, which reflect nonuniform, often unpredictable patterns of neoplastic differentiation. When this introduction was written (1987), new technics of flow cytometry, in situ DNA hybridization, and development of monoclonal antibodies for immunoperoxidase studies were evolving and contributing to the identification and classification of human liver tumors. It is increasingly clear that variability in histologic patterns as well as other functional and behavioral features are not apparent unless special efforts are taken to look for such variation. Accurate classification of human tumors requires adequate sampling and examination, and the general guideline of one paraffin block per centimeter of tumor diameter is advisable (Weinberg and Finegold). Interpretation of flow cytometry is in its infancy and its application to routine tumor classification has not yet been proved. It is clear, however, that routine light microscopy has shortcomings and that additional data including electron microscopy, immunoperoxidase stains, biochemical analysis, and special technics, such as flow cytometry and in situ hybridization, may be useful in diagnosis and prognosis.

Classification of human tumors remains based on the concept that the cell of origin produces similar-appearing cells; however, malignant tumors may exhibit a spectrum of metaplasia and differentiation not traditionally associated with a specific tumor. Experimentally, a spectrum of tumors with a wide variety of histologic patterns, including hepatoblastoma, hepatocellular carcinoma, cholangiocarcinoma, as well as epidermoid carcinoma, adenocarcinoma, and sarcoma, has been produced from a single neoplastic cell line (Tsao and Grisham). Some monoclonal sarcomas demonstrated both osteoid and chondroid stroma rather than only one type of morphologic pattern.

Although most human neoplasms seem relatively constant in their morphologic appearance, it is uncertain to what extent this may be merely a result of incomplete sampling. Nonetheless, it remains convenient

to categorize tumors based on the predominant histologic pattern. Most tumors remain homogenous during their course, even with various treatment plans, and thus the prognosis remains somewhat predictable.

EMBRYOLOGY AND TUMOR CLASSIFICATION

A review of the embryology of hepatic development assists in the classification of hepatic tumors. Therefore, a short summary of hepatic development indicating the source of various hepatic cell types is presented to assist in the understanding of tumor classification. Primary hepatic neoplasms may arise from any of multiple cell types within the liver including: the hepatocytes; bile duct epithelium; hilar periductal glands; neuroendocrine cells; a variety of mesodermal cells including endothelium; sinusoidal lining cells such as Kupffer cells and Ito cells; lymphoid cells; fibroblasts; nerve and smooth muscle cells; as well as ectopic tissue. The following summary is based on human studies by several investigators including Enzan and associates; Koga; Severn; and Streeter.

In the 16 somite embryo, when the fetus is about 3 mm long, the endodermal anlage of the liver forms a ventral outpouching of the primitive foregut. The hepatic anlage is abutted against the mass of undifferentiated mesenchyme of the septum transversum situated just caudal to the heart and in front of the yolk sac (figs. 1 and 2). The mesoblastic tissue of the septum transversum is derived from the coelomic tract and its earliest differentiation is toward the formation of angioblasts. Subsequently, this mesenchymal tissue from the septum transversum gives rise to Kupffer cells and Ito cells which line the sinusoids of the human liver (Enzan et al.).

Figure 1
(Figures 1 and 2 are from the same patient)
EMBRYOLOGY
Liver and heart regions in a 16 somite embryo are illustrated. X100.* (Fig. 2 from Fascicle 25, First Series.)

* Hematoxylin and eosin stain has been used throughout the Fascicle unless otherwise stated.

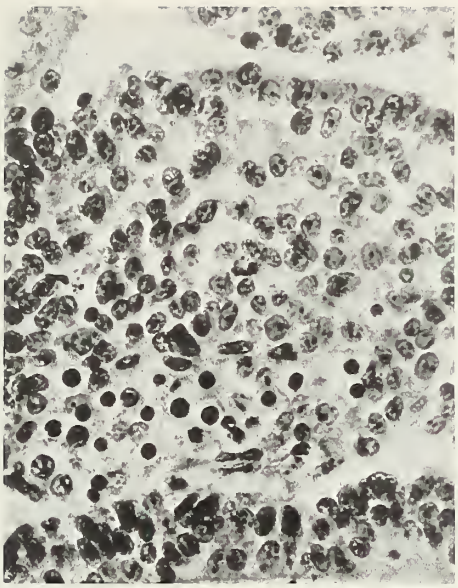

Figure 2
EMBRYOLOGY
Higher magnification of the area enclosed by white lines in Figure 1. This is the liver primordium with cells forming the framework proliferating at the coelomic surface and some cells in the first steps of angiogenesis. Below is the intestinal epithelium, which is not yet forming epithelial cords. X400. (Fig. 3 from Fascicle 25, First Series.)

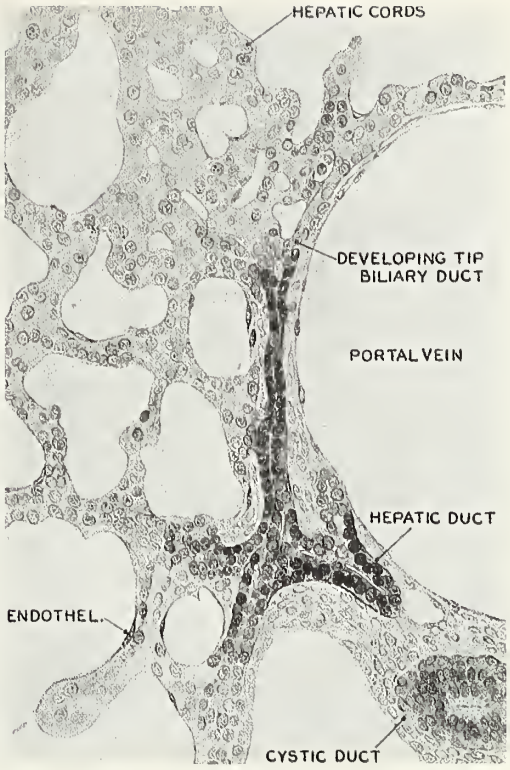

Figure 3
EMBRYOLOGY
A 14 mm embryo with abrupt transition of biliary ducts to the hepatic epithelium. This area shows the tips of ducts merging with hepatic epithelium and redifferentiating into the compact, deeply staining, duct-forming cells. This process of redifferentiation of hepatic epithelium extends outward through the embryonic connective tissue coat of the portal vein and its branches. The growth of new connective tissue and formation of ducts proceeds concurrently. X250. (Fig. 4 from Fascicle 25, First Series.)

A separate anlage gives rise to the entire epithelial portion of the biliary tree, gallbladder, and liver parenchyma. Primitive endodermal cells sprout from the ventral and lateral walls of the hepatic diverticulum and invade the primitive septum transversum mesenchyme. At the same time, there is rapid angiogenesis in the mesenchyme with formation of the sinusoids which become the chief blood forming organ in the embryo. As the liver continues to develop, the bile ducts penetrate into the mass of liver-sinusoid tissue. In the 12 mm embryo, the bile ducts extend only a short distance into the hilar area where they are intimately associated with blood vessels and highly cellular connective tissue. Channels lined with bile duct epithelium fade imperceptibly into tiny canaliculi lined with pink-staining liver cells. Streeter suggested that the bile duct cells do not transform into liver parenchymal cells, but that the existing parenchymal cord cells change into a bile duct type of cell (fig. 3). This occurs in conjunction with the ingrowth of the mesenchyme of the portal tracts. Bile duct epithelium is seen on one side of a duct where it is in contact with

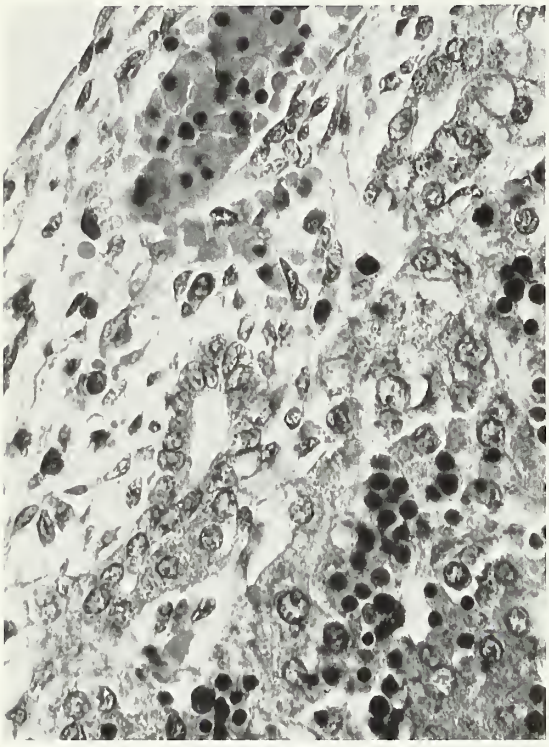

Figure 4
EMBRYOLOGY

Section through a large portal tract near the hilum of the liver in a 45 mm embryo. Two bile ducts are present on the right. In the lower duct, the epithelium in contact with the mesenchyme is of the bile duct type, while that in contact with the sinusoid is of the liver cell type. Finely granular material in the cytoplasm of the latter cells is presumably bile. X450. (Fig. 5 from Fascicle 25, First Series.)

connective tissue and liver cells bordering upon sinusoids complete the circumference of the duct (fig. 4). Following this redifferentiation of liver cells to interlobular ducts, they are, even in diseased states, considered unable to form functioning hepatic parenchymal units. If this concept is correct, carcinoma arising from liver cells may, in the presence of mesenchymal tissue, form bile duct components; but it is not clear what stimulus, if any, would transform tumors arising from bile ducts into liver cell units. It is possible that limited capacity for conversion might exist in bile duct carcinomas arising from interlobular ducts that had embryologically once been hepatic cords, but tumors originating from major ducts, which had never gone through a stage of hepatic cords, may be incapable of transformation to the more differentiated hepatocellular stage.

Mixed hepatocellular-bile duct carcinomas may arise from cholangiolar cells. Although the transition between cholangioles and peripheral intralobular bile canaliculi is clear, these cholangiolar cells may transform into both hepatocytes and bile duct epithelium.

Mesenchymal tissue of the septum transversum develops as a continuation of the mesenchyme of the yolk sac and has the same capacity for angiogenesis and hematopoiesis as the yolk sac mesenchyme (Severn). The hematopoietic islands develop early in the liver subsequent to the development of similar islands in the yolk sac. Thus, of persisting adult organs, the liver is the earliest organ of hematopoiesis and retains the potential for production of lymphocytes. T lymphocyte precursors are identified in human embryos at 12 to 17 weeks (Pyke and Gelfand). Lymphoid neoplasms originating in the liver are very rare, but hepatic involvement by lymphoma-leukemia initially occurs in portal areas, the site of the more primitive mesenchymal tissue. Kupffer cells appear derived from circulating macrophages from the yolk sac. The Ito cells appear morphologically similar to fibroblasts and seem to share a common origin from the septum transversum (Enzan et al.).

Neuroendocrine tumors are rarely encountered in the liver and biliary tree, but their presence indicates that the scattered

neuroendocrine cells within the biliary tree are capable of producing a hepatic tumor, just as occurs in more common locations, such as the pancreas. These precursor cells apparently are not of neural crest origin, but are the result of redifferentiation of endodermally derived cells.

The liver gives rise to tumors composed of derivatives of more than one primitive germ cell layer, including mature or primitive bone, cartilage, muscle, and epithelium. Such neoplasms are given a variety of names, including mixed or teratoid tumors, and the most prominent group is the hepatoblastoma in infants and young children. Whether these hepatoblastomas are truly teratomatous or derived from a single germ cell component (i.e., epithelial neoplasia with mesenchymal metaplasia) is currently debated. A few rare teratomas have been reported, as well as other unusual but classic malignant germ cell tumors, such as yolk sac carcinoma.

INCIDENCE OF HEPATIC TUMORS

Table 1 illustrates the relative incidence of primary hepatic tumors in selected populations. An autopsy survey from a large indigent population (LACUSC-MC) combined with the autopsy survey of the physically separate USC Liver Unit, a referral unit that receives selected liver disease patients from the larger unit (LACUSC-MC), is noted in column A (autopsy). Column B is a survey conducted through the Cancer Surveillance Program of all primary hepatic tumors, including all surgical and autopsy material, identified in Los Angeles County at all private, governmental, and teaching hospitals. Histologic slides from all hospitals were reviewed by the liver pathology staff. A greater number of benign tumors were identified in the autopsy population, which reflects that these tumors often are incidental findings and do not produce clinical symptoms.

Table 1

INCIDENCE OF PRIMARY HEPATIC TUMORS†
LACUSC MEDICAL CENTER AND LOS ANGELES COUNTY HOSPITAL

Type	(A) LACUSC MEDICAL CENTER* No.	Percent	(B) LOS ANGELES COUNTY** No.	Percent
Benign	**64**	**11.9**	**16**	**5.8**
Bile duct adenoma	16	3.0	5	1.8
Hepatocellular adenoma	5	0.9	4	1.4
Focal nodular hyperplasia	42	7.8	7	2.5
Inflammatory pseudotumor	1	0.2	0	0
Malignant Epithelial	**462**	**86.2**	**258**	**93.1**
Hepatocellular carcinoma	414	77.2	228	82.3
Typical	388	72.3	207	74.7
Sclerosing	15	2.8	10	3.6
Fibrolamellar	5	0.9	4	1.4
Giant cell	2	0.4	1	.4
Undifferentiated	3	0.6	3	1.1
Spindle cell	1	0.2	3	1.1
Hepatoblastoma	2	0.4	3	1.1
Cholangiocarcinoma	44	8.2	27	9.7
Hilar	14	2.6	7	2.5
Peripheral	30	5.6	20	7.2
Carcinoid	2	0.4	0	0
Malignant Mesenchymal	**10**	**1.9**	**3**	**1.1**
Endothelial	4	0.8	1	.4
Angiosarcoma	2	0.4	1	.4
Epithelioid hemangioendothelioma	2	0.4	0	0
Lymphoma (primary)	1	0.2	0	0
Undifferentiated embryonal sarcoma	5	0.9	2	.7
Total	**536**	**100**	**277**	**100**

† Excluding benign hemangiomatous lesions
* LACUSC Medical Center and USC liver autopsies 1918-1982, 96,625 autopsies
** Cancer Surveillance Project — All primary hepatic tumors in Los Angeles County hospitals (private and public) in 2 year period (1977-1978)

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BENIGN EPITHELIAL TUMORS AND TUMOR-LIKE CONDITIONS

HEPATOCELLULAR HYPERPLASIA

Hepatocellular hyperplasia has been divided into several categories and some of the groups overlap with previous definitions of these conditions. We have attempted to organize the lesions into groups based on whether the lesion is focal or diffuse, small or large, or related to underlying chronic liver injury. Table 2 gives the major diagnostic groups and the criteria for inclusion. Classification of specific patients may still be difficult, as some lesions may have features of more than one diagnostic group.

MACROREGENERATIVE NODULE

SYNONYMS AND RELATED TERMS: Adenomatous hyperplasia; adenomatoid hyperplasia; multiple nodular hyperplasia; cirrhotic pseudotumor.

Definition. Macroregenerative nodule, commonly called adenomatous hyperplasia, is a large (greater than 1 cm in diameter), distinct, well-circumscribed nodule composed of hepatocytes arranged in normal cords and contains several portal areas (Edmondson). Macroregenerative nodule arises in two settings: severe acute hepatic injury, as in submassive hepatic necrosis; or chronic liver disease, such as advanced cirrhosis.

Table 2

COMPARISON OF HYPERPLASTIC HEPATOCELLULAR CONDITIONS

Criteria	Focal Nodular Hyperplasia	Hepatocellular Adenoma	Nodular Regenerative Hyperplasia	Multiple Hepatocellular Adenoma	Macroregenerative Nodule
Gross	Scar	Hemorrhage, necrosis	Bulging nodules	Bulging nodules	Bulging nodules
Number of Lesions	1 (90%)	1 (90%)	Many	Many	Many or few
Size (average range)	1-6 cm	4-12 cm	< 1.5 cm	2-8 cm	1-6 cm
Key Feature	Pseudoductules	Neohepatocytes	Small nodules	Normal cords	Portal tracts
Prior Liver Disease	None	None	None	None	Submassive hepatic necrosis or cirrhosis
Associated Etiology	None	Estrogen, anabolic steroids	Vascular disease	None	None

Incidence. Macroregenerative nodule occurs in less than 2 percent of cases of submassive hepatic necrosis. Sasaki reported finding macroregenerative nodule in 10.8 percent of cirrhotic liver, although we have observed it only rarely in cirrhosis (less than 1 percent). Careful and thorough examination of thin (4 mm) whole liver slices indicated a 14 percent incidence of macroregenerative nodule in chronic liver disease in a series of 345 autopsy patients (Furuya et al.).

Clinical. The complications of portal hypertension may be evident in the setting of either severe acute injury (massive hepatic necrosis) or advanced cirrhosis. No specific clinical symptoms are attributable to macroregenerative nodule distinct from the associated severe hepatic condition. However, clinical evaluation by specialized technics may reveal the lesion. At peritoneoscopy, or by radiographic or ultrasound studies, the large nodule(s) may resemble tumor. Their discovery is often the result of a follow-up of a patient suspected of developing carcinoma (Arakawa et al.; Rabinowitz et al.).

Pathogenesis. Macroregenerative nodule occurs in the setting of marked regenerative stimulus provided either by massive hepatic necrosis or chronic hepatocellular destructive activity with cirrhosis. However, only a small proportion of patients with extensive hepatocellular destructive disease develop macroregenerative nodules. Factors that seem to promote macroregenerative nodules are prolonged survival with severe liver disease and, perhaps, failure of remaining hepatic tissue to respond to the regenerative stimulus. Arakawa and associates speculated that this condition is preneoplastic in the patient with cirrhosis.

Gross. Macroregenerative nodules present as single or multiple nodules that are 1 to 12 cm in diameter and are bright orange, bulging masses separated by collapsed purple stroma in the setting of massive hepatic necrosis (pl. I-A; figs. 5, 6). In the advanced cirrhotic liver, these nodules may be bile-stained and bulging, but tend to be smaller and range in size from 2 to 8 cm in diameter (fig. 6). Necrosis and hemorrhage are not seen unless shock occurred as a terminal event.

Microscopic. The large hyperplastic masses of hepatocytes form cords of liver cells that are one to two cells in thickness. The cells appear normal, without dysplastic changes. The nodule includes small bile ducts and portal vessels, usually at the margins (figs. 7-9). A true capsule is not present, but the compressed adjacent portal areas may appear as a pseudocapsule.

Figure 5
MACROREGENERATIVE NODULE
This cut surface of liver with a close-up of macroregenerative nodules forming multiple bulging nodules of bright orange liver contrasts the adjacent depressed, dark purple, collapsed liver (not visible in figure), in a patient with submassive hepatic necrosis. (Fig. 11 from Benign Epithelial Tumors and Tumor-Like Lesions of the Liver. In: Hepatocellular Carcinoma. Okuda, K. and Peters, R.L. [Eds.]. New York: John Wiley & Sons, 1976.)

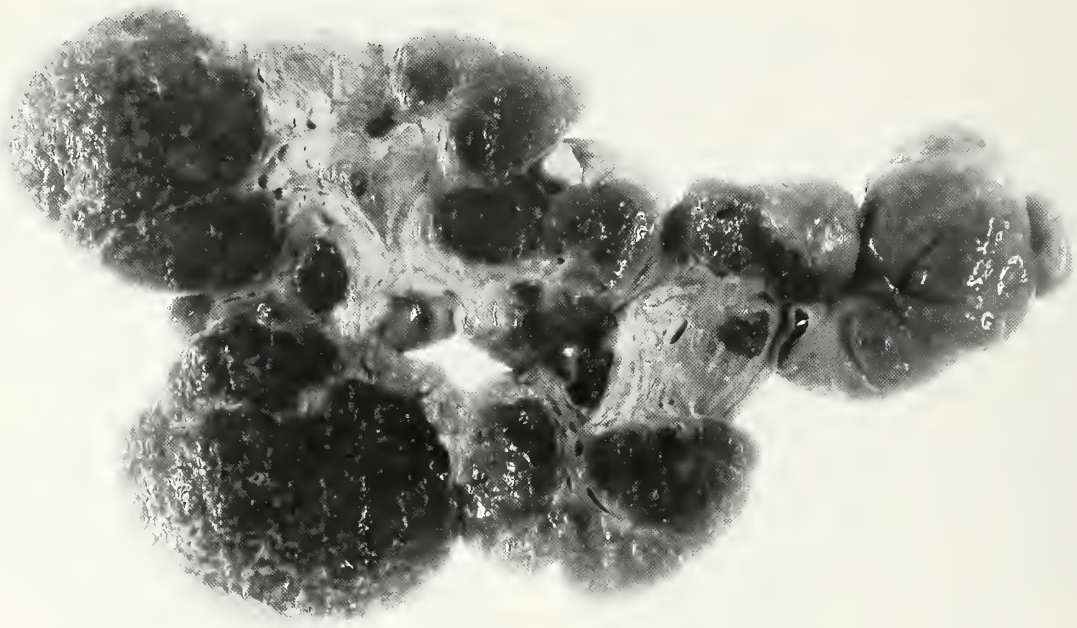


Figure 6
(Figures 6 and 9 are from the same patient)
MACROREGENERATIVE NODULE

Large macroregenerative nodules in cirrhosis and collapse with broad fibrous bands secondary to submassive hepatic necrosis are seen in this external surface of liver. This is an exaggerated example, with large macroregenerative nodules, in a 46 year old man with cirrhosis, probably alcoholic type, superimposed acute viral hepatitis (Type HAV), with consequent submassive hepatic necrosis and prolonged clinical course. The patient had ascites and splenomegaly, and died with bleeding esophageal varices. The liver weight was 1375 g and the nodules measured up to 6 cm. (Courtesy of Dr. Gary Kanel, Downey, California.)

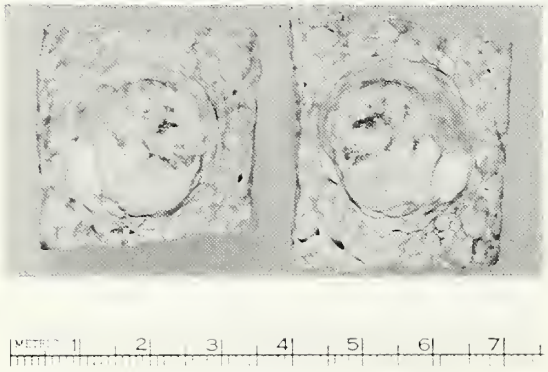


Figure 7
(Figures 7 and 8 are from the same patient)
MACROREGENERATIVE NODULE

A cut surface of cirrhotic liver shows bulging macroregenerative nodule. (Fig. 12 from Benign Epithelial Tumors and Tumor-Like Lesions of the Liver. In: Hepatocellular Carcinoma. Okuda, K. and Peters, R.L. [Eds.]. New York: John Wiley & Sons, 1976.)

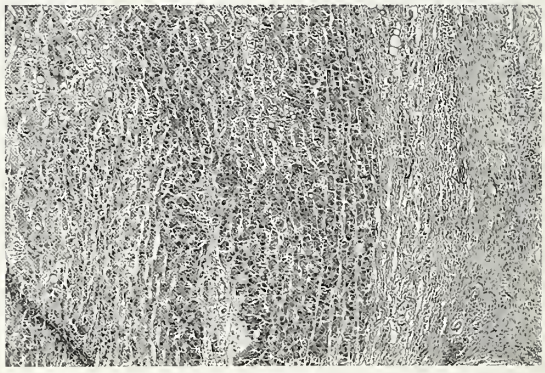


Figure 8
MACROREGENERATIVE NODULE

Macroregenerative nodule is expanding and pushing the adjacent liver. The hyperplastic nodule containing intact portal structures is noted in this figure. X75. (Fig. 13 from Benign Epithelial Tumors and Tumor-Like Lesions of the Liver. In: Hepatocellular Carcinoma. Okuda, K. and Peters, R.L. [Eds.]. New York: John Wiley & Sons, 1976.)

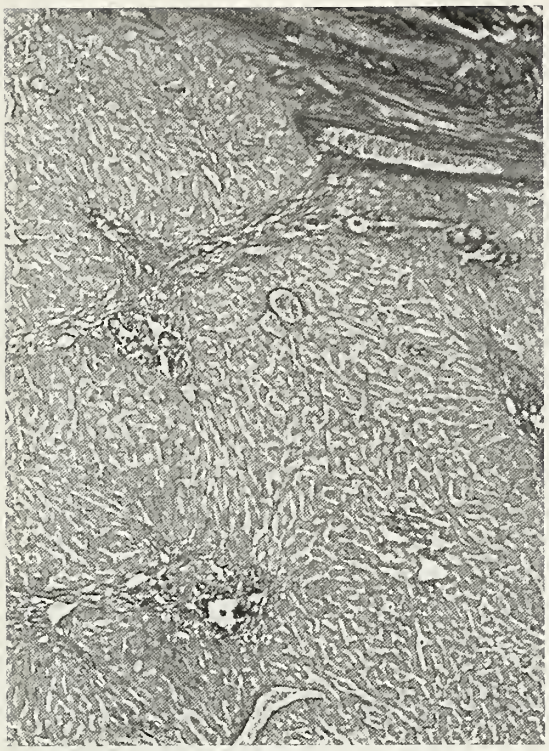


Figure 9
MACROREGENERATIVE NODULE
This is a macroregenerative nodule in a cirrhotic liver with large areas of collapse, forming fibrous bands. Within the large nodule are multiple portal areas. Reticulin stain. X125. (Courtesy of Dr. Gary Kanel, Downey, California.)

Differential Diagnosis. In contrast to hepatocellular carcinoma, macroregenerative nodule is composed of thin cell plates (1-2 cells), and, although nucleoli may be prominent, lacks dysplastic features, mitosis, vascular invasion, expansile growth into adjacent liver, and a nodule-within-nodule growth pattern. Hepatocellular adenoma is distinguished from macroregenerative nodule by the absence of portal areas with small bile ducts, hepatic arterioles, and portal veins. Furthermore, hepatocellular adenoma does not seem to occur in the setting of severe hepatic necrosis or cirrhosis. Nodular regenerative hyperplasia, unlike macroregenerative nodule, is diffuse and composed of smaller lesions that do not incorporate portal structures within the nodule. Angiographic study reveals that macroregenerative nodule is hypovascular (Sasaki).

NODULAR REGENERATIVE HYPERPLASIA

SYNONYMS AND RELATED TERMS: Nodular transformation; noncirrhotic nodulation; hepatocellular adenomatosis; adenomatous hyperplasia; diffuse nodular hyperplasia.

Definition. Nodular regenerative hyperplasia is diffuse nodularity of the liver produced by many regenerative nodules that are not associated with any fibrosis (Steiner).

Incidence. Nodular regenerative hyperplasia is relatively rare with approximately one-third the number of cases reported as for focal nodular hyperplasia. The largest published series includes 30 cases from the AFIP records (Stromeyer and Ishak).

Clinical. Nodular regenerative hyperplasia is often an incidental finding at autopsy or, in many patients, is discovered because of portal hypertension and its complications, such as bleeding esophageal varices or ascites. Nodular regenerative hyperplasia is associated with a variety of diseases, including rheumatoid arthritis; Felty's syndrome; subacute bacterial endocarditis; multiple myeloma; macroglobulinemia; myelofibrosis; polycythemia vera; hereditary hemorrhagic telangiectasia (Wanless and Gryfe); a variety of drugs (Ishak); polyarteritis nodosa (Nakanuma et al.); diabetes mellitus (Thung et al.); and the toxic oil syndrome (Solis-Herruzo et al.).

Pathogenesis. Wanless and Gryfe have reported that in nodular regenerative hyperplasia many intrahepatic branches of the portal vein are occluded and thus it mimics idiopathic portal hypertension. The latter condition has an irregular arrangement of the lobules, but no true nodularity. In our limited material, the portal vein and hepatic vein branches of idiopathic portal hypertension are not occluded. However, the multiple diseases associated with nodular regenerative hyperplasia frequently produce vascular changes. A patient with systemic rheumatoid arteritis developed nodular regenerative hyperplasia and, at autopsy, the portal venous branches were diminished (Reynolds and Wanless). Thus, the hepatic arterial inflammation may secondarily involve the portal venous branches and stimulate nodular hepatocellular growth. A striking example of nodular regenerative hyperplasia occurred in a patient with systemic lupus erythematosus, which usually spares the liver, but does involve vessels in other organs (fig. 10).

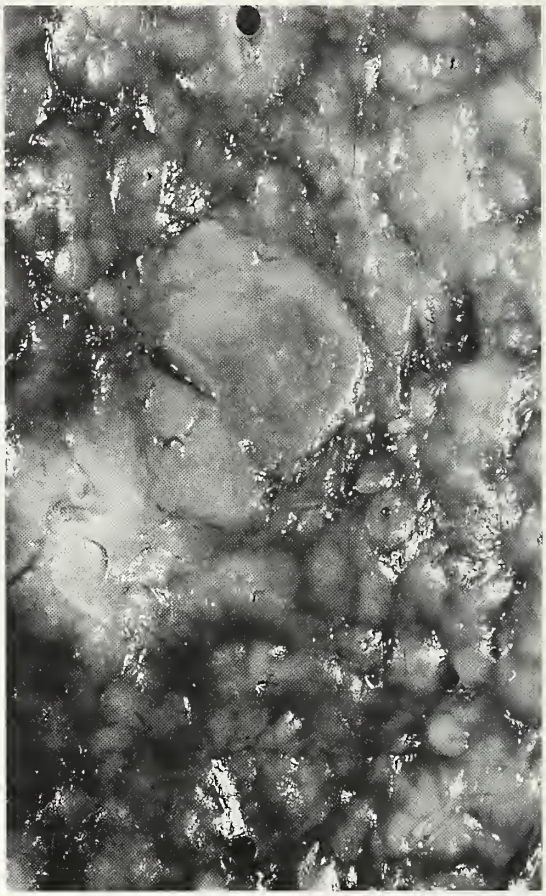


Figure 10
NODULAR REGENERATIVE HYPERPLASIA
This cut surface of nodular regenerative hyperplasia with many small, round, bulging nodules is from a 41 year old woman with lupus erythematosus, ascites of unknown cause (until the autopsy), and normal serum hepatic tests. The gross appearance resembled a cirrhotic liver, but there was little resistance to cutting, indicative of the lack of fibrosis.

Gross. Multiple bulging nodules are noted on the external surface, and the cut surface of the liver has multiple bulging, or flat but discrete, nodules that resemble metastatic carcinoma. These nodules vary from a few millimeters to 1 cm in greatest dimension, are widely scattered (pl. I-B), and have a slightly paler color than the intervening liver. Although usually diffuse, in three of 30 patients, the nodules were limited to part of the liver (Stromeyer and Ishak).

Microscopic. In typical patients, the regenerative nodules are the size of a lobule. The growth pattern noted at low power is distinctive, as the bulging nodules distort the adjacent lobules and no fibrosis is noted. These hyperplastic foci may be periportal and surround a portal area or be eccentric (fig. 11). The reticulum stain demonstrates the hyperplastic bulging growth pattern best (fig. 12). In some nodules, marked hepatocellular dysplasia has been noted (Stromeyer and Ishak), but is unusual (Wanless et al., 1981).

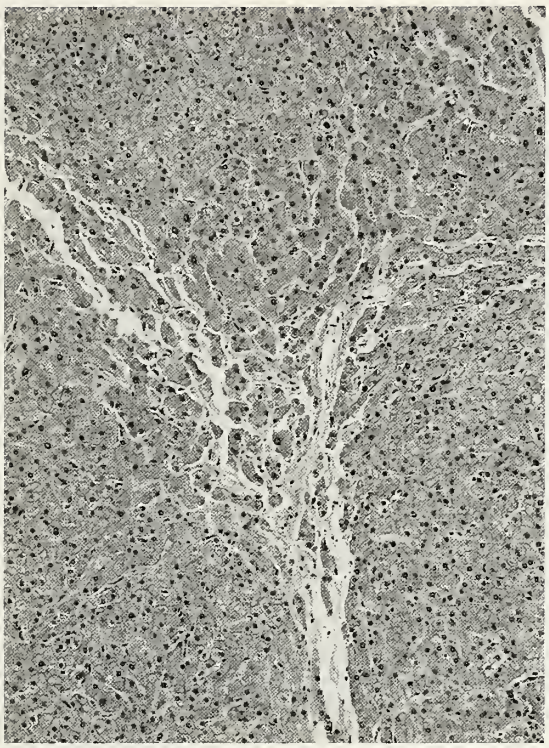


Figure 11
(Figures 11 and 12 are from the same patient)
NODULAR REGENERATIVE HYPERPLASIA
Nodular regenerative hyperplasia has multiple small nodules of hepatocytes in thin cords. The nodularity is most easily noted at very low power. X310. (Courtesy of Dr. Kenneth Frankel, Covina, California.)

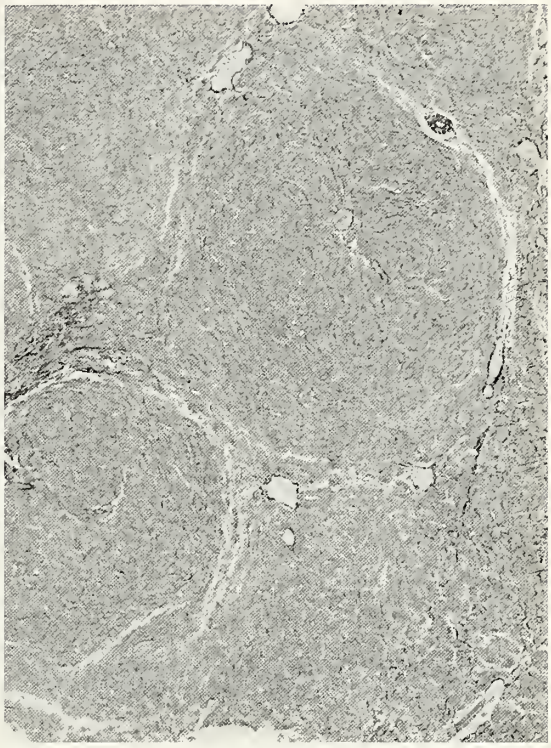


Figure 12
NODULAR REGENERATIVE HYPERPLASIA
A reticulin stain accentuates the nodular growth pattern of nodular regenerative hyperplasia. The reticulin fibers are arranged in nodules that seem to bulge or expand. X125. (Courtesy of Dr. Kenneth Frankel, Covina, California.)

Differential Diagnosis. Upon gross inspection of the liver, metastatic carcinoma is the prime consideration because of the striking diffuse nodularity in an otherwise normal liver. By light microscopy, carcinoma is easily dismissed because the nodules are hepatocytes. Macroregenerative nodules are distinguished by the smaller size of the lesions in nodular regenerative hyperplasia and the origin of macroregenerative nodule in abnormal liver, such as cirrhosis or massive necrosis. Partial nodular transformation is limited to the hilar area and has a wider range in nodule size.

PARTIAL NODULAR TRANSFORMATION

Partial nodular transformation is a rare condition with less than 20 patients described by 1985 (Wanless et al., 1985a). Partial nodular transformation is the presence of hepatocellular nodules of varying size (3-40 mm) located in the perihilar area and associated with portal hypertension (fig. 13). The presence of ascites and esophageal varices often brings the patient to medical care (Sherlock et al.). Portal hypertension is documented, but the etiology of the increased portal pressure is not apparent. Morphometric analysis reveals a

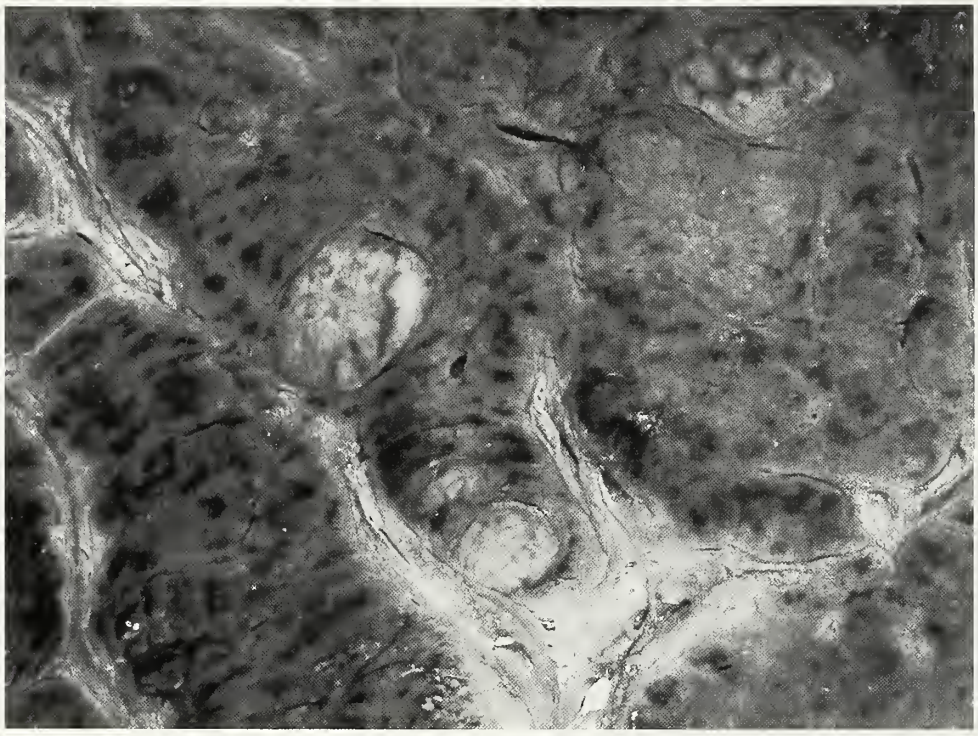


Figure 13
PARTIAL NODULAR TRANSFORMATION

This is a cut surface of a liver with four nodules and congestion of intervening liver in a 29 year old man with patent ductus venosus and partial nodular transformation of the liver. (Fig. 2 from Wanless, I.R., Lentz, J.S., and Roberts, E.A. Partial nodular transformation of liver in an adult with persistent ductus venosus. Review with hypothesis on pathogenesis. Arch. Pathol. Lab. Med. 109:427-432, 1985.)

marked decrease in the size and number of small portal vein branches in portal areas compared to control livers (Wanless et al., 1985a). Wanless and associates (1985a) have proposed that thrombosis of major portal vein branches results in recanalization, which provides portal blood supply to the perihilar hepatocytes and is the regenerative stimulus for the nodular growth.

FOCAL NODULAR HYPERPLASIA

SYNONYMS AND RELATED TERMS: Focal cirrhosis; hamartomatous cholangiohepatoma; hepatic hamartoma; solitary hyperplastic nodule.

Definition. Focal nodular hyperplasia is a well-circumscribed, usually solitary mass characterized by a central fibrous scar with surrounding nodules of hyperplastic hepatocytes and small bile ductules. No normal portal structures are noted, although major vessels course through the tumor and are prominent in the fibrous scar.

Incidence. Focal nodular hyperplasia is the most common benign hepatic tumor (excluding vascular tumors), comprising approximately 8 percent of all primary hepatic tumors in the autopsy survey of LACUSC Medical Center and the USC Liver Unit. However, in the consultation files at USC, focal nodular hyperplasia and

hepatocellular adenoma were nearly equal in number during the period 1960-1980, during which 48 cases were recorded. The largest published series was 130 cases in 1975 (Ishak and Rabin).

Clinical. Although focal nodular hyperplasia is usually an incidental finding at autopsy or elective surgery, up to one-third are discovered because of clinical symptoms. In our files, only 11 of 41 women with focal nodular hyperplasia had symptoms or a palpable mass. Focal nodular hyperplasia is predominantly a lesion of young women; in most series the average age was in the thirties. There is at least a 2:1 female preponderance. Radiographic distinction of focal nodular hyperplasia from hepatocellular adenoma may be difficult if one relies on ultrasound or nuclear scans.

Pathogenesis. Several theories for etiology have been proposed, but the most likely mechanism is presented by Wanless and associates (1985b). They reviewed 51 lesions in 36 patients, examined serial sections, and reconstructed models in selected lesions. Morphometric analysis indicated that an anomalous arterial branch, unaccompanied by portal venous branches or ducts, fed numerous small nodules comprising the focal nodular hyperplasia lesion. The frequent coexistence of focal nodular hyperplasia with other vascular and neuroendocrine anomalies suggested that the vascular malformation was developmental in origin and led to hepatocellular hyperplasia. Butron Vila and colleagues have proposed that the ductular component is not a proliferation of preexisting bile ductules, but the result of hepatocellular metaplasia. Other theories of origin include focal inflammatory reaction and hamartoma. Because the lesion is common in young women, the association with oral contraceptive use has been studied. In 4 of our 41 consultation patients, there was oral contraceptive use documented and all four had multiple lesions. Two patients had prominent lipochrome pigment, which is a feature seen in some hepatocellular adenomas occurring in women on oral contraceptives, but absent in women not on the "pill". The presence of focal nodular hyperplasia in children and men, and the use of the pill in only a few of the women patients, indicates that estrogen is not likely responsible for the development of the lesion (Knowles et al.).

Gross. Focal nodular hyperplasia is usually a solitary nodule (80 to 95 percent) and visible from the capsular surface (fig. 14). Occasionally, focal nodular hyperplasia is located deep within the liver or is pedunculated. Although either lobe of the

Figure 14
FOCAL NODULAR HYPERPLASIA
A dimpled external surface of focal nodular hyperplasia shows the central retraction by fibrous tissue and the bulging nodules.

liver may be involved, approximately two-thirds occur in the right lobe. The majority of lesions have a central fibrous scar, especially if they are larger than 1 cm. The size of focal nodular hyperplasia varies from less than 1 cm to as large as 15 cm, although in most series the majority of lesions are less than 5 cm in maximum diameter (Ishak and Rabin; Kerlin et al.). The lesion bulges from the cut surface and is usually a lighter tan than the adjacent normal liver (fig. 15). The margin is sharp and no capsule is present (95 percent). Hemorrhage and necrosis are rare and thin septae radiate from the central scar, dividing the lesion into lobules.

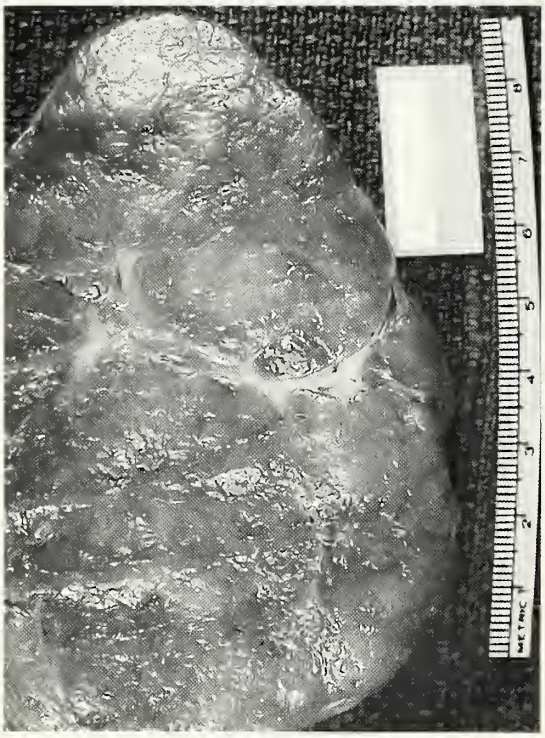


Figure 15
FOCAL NODULAR HYPERPLASIA
The cut surface of focal nodular hyperplasia shows a central fibrous scar and radiating fibrosis that divides the bulging nodules of tan liver.

Microscopic. The central fibrotic zone is dense connective tissue which contains blood vessels with thick, often myxomatous, walls (figs. 16, 17). Many thick-walled arteries are present along the thin septae extending from the center to the periphery. Within the fibrous septae and among the hepatocytes there is bile ductular proliferation (fig. 18). Transition of hepatocytes within the lesion to the small bile ductular units suggests that these ductular units are due to metaplasia of hepatocytes. Most lesions have variable numbers of lymphocytes or polymorphonuclear leukocytes within the thin fibrous septae. Fatty change occurs in some lesions and bile formation is rare. Hyperemia of sinusoids in the adjacent liver is frequent.

Figure 16
FOCAL NODULAR HYPERPLASIA
This is a thick myxomatous wall of central vessels in a fibrous scar of focal nodular hyperplasia. X30. (Courtesy of Dr. Weldon K. Bullock, California Tumor Tissue Registry.)

Figure 17
(Figures 17 and 18 are from the same patient)
FOCAL NODULAR HYPERPLASIA
A dense central fibrous scar of focal nodular hyperplasia has radiating fibrous bands containing major vessels. Small fibrous bands extend into hepatic cords with many small bile ductules at the margin of the stroma and hepatocytes. This was an incidental polypoid nodule of the left lobe of liver in a woman with known breast carcinoma and pancreatic mass suspected of being carcinoma. X125. (Courtesy of Dr. Paul Hanson, Pasadena, California.)

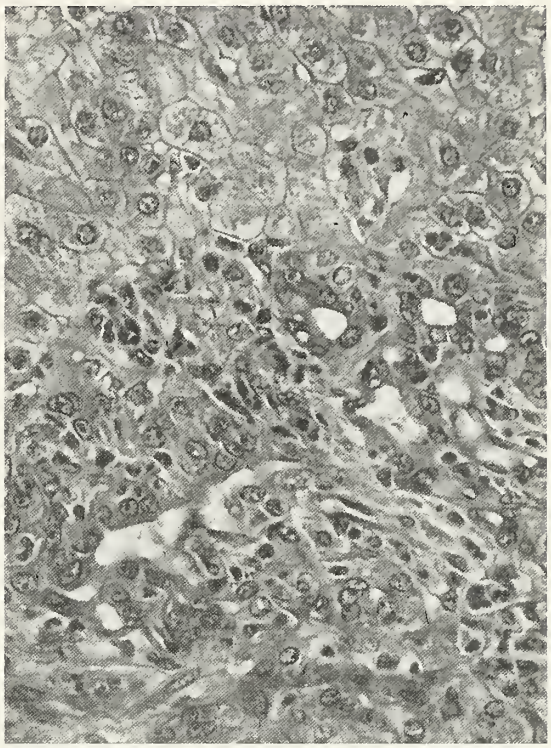


Figure 18
FOCAL NODULAR HYPERPLASIA
Numerous bile ductules appear to be metaplastic hepatocytes and occur in "islands" within the nodules of hepatocytes. Note the absence of portal vessels (such as arteriole or vein) in the mass of proliferated ductules. X1240. (Courtesy of Dr. Paul Hanson, Pasadena, California.)

Differential Diagnosis. A solitary hepatic nodule may be hepatocellular adenoma, mixed hamartoma, metastatic tumor, inflammatory pseudotumor, bile duct adenoma, or hepatocellular carcinoma. The presence of a central scar and the small bile ductular structures are the diagnostic features of focal nodular hyperplasia. Hepatocellular adenoma is usually larger than focal nodular hyperplasia, often has hemorrhage and necrosis, lacks the central scar and bile ductular units, and often has a thin capsule. Mixed hamartoma is distinguished by an abundance of fibrous tissue within which proliferated bile duct units are present. Metastatic carcinoma is readily distinguished by microscopic examination. If a frozen section is utilized, search for the proliferated bile ductules will exclude metastatic carcinoma easily and allow recognition of focal nodular hyperplasia. Hepatocellular carcinoma is distinguished by the presence of a solid growth pattern with cell plates more than two cells in thickness, often shows

dysplasia, and demonstrates invasive features characterized by spread into the adjacent hepatic lobules. Because the fibrolamellar variant of hepatocellular carcinoma also has a central fibrous scar, it has gross similarities to focal nodular hyperplasia. However, by microscopy, the pattern of fibrosis is different, being composed of thin "lamellar" strands, and the tumor cells are recognizably malignant because they are larger than the adjacent normal hepatocytes, have large nucleoli, and have mitoses.

Variants. Childhood focal nodular hyperplasia accounts for approximately 20 percent of reported cases. The age ranges from newborn and spans each decade evenly (Stocker and Ishak). Female predominance (70 percent) is noted among children as well as adults. In the largest published pediatric series, the distribution of lesions favored the left lobe (60 percent), with 30 percent in the right lobe, and 10 percent in both; other published reports, however, did not show a similar left lobe predominance. Large lesions of up to 15 cm were reported. Broad central scars were present in half of the lesions.

Prognosis. Transformation of focal nodular hyperplasia to carcinoma is unknown to us, although some published references consider the fibrolamellar variant of hepatocellular carcinoma related to focal nodular hyperplasia. We are unaware of convincing evidence of transition of a focal nodular hyperplasia to malignancy. Biopsy (open or needle) may establish a reliable diagnosis and resection is not mandatory. The bleeding risk associated with oral contraceptives is uncertain, thus patients may be advised to avoid oral contraceptives.

MIXED HAMARTOMA

SYNONYMS AND RELATED TERMS: Mixed adenoma of the liver.

Definition. Mixed hamartoma is a solitary tumor composed of both proliferating hepatocytes and bile ductular structures in dense fibrous tissue. The lack of vascular structures adjacent to the bile ductular units indicates that true portal structures are not present in the tumor.

Incidence. Although five examples had been reported by 1978 according to Rhodes and associates, other reported cases are probably included in series of focal nodular hyperplasia, but insufficient histologic detail and descriptions do not allow identification by reading the reports (Rhodes et al.).

Clinical. The tumors are usually detected at a young age. Three of the five patients were 3 to 7 months of age and the other two, 23 and 13 years old (Benson and Penberthy; Franklin and Downing; Kay and Talbert; Rhodes et al.). There is no sex predilection and the presence of a mass is the primary reason for discovery in the younger patients. One patient experienced recurrent abdominal pain with anorexia, nausea, and vomiting and was found to have a very large tumor replacing the left lobe and half of the right lobe (Kay and Talbert).

Pathogenesis. The stimulus for hepatocellular proliferation is unknown, but the fibrous tissue appears to coincide with the transformation of hepatocytes into ductular elements (Rhodes et al.).

Gross. Mixed hamartoma has a bulging external surface (fig. 19). The cut surface reveals multiple nodules with white centers separated by thin fibrous bands. One large tumor, 20x10x6 cm, was attached to

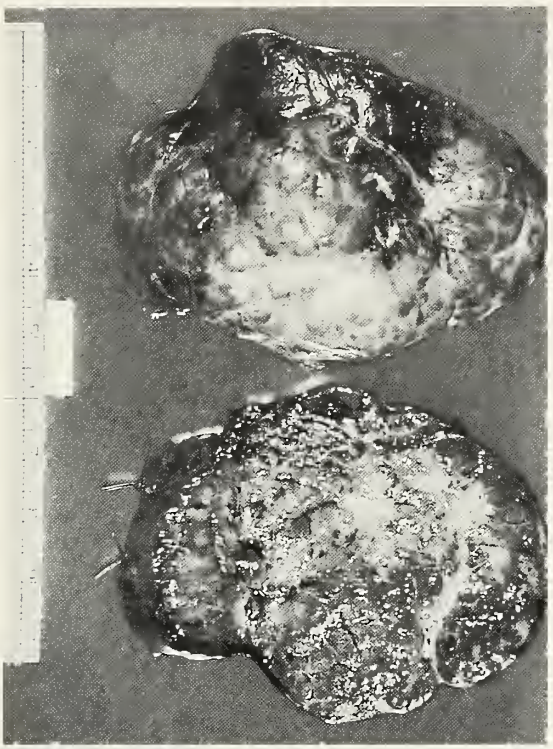


Figure 19
(Figures 19-21 are from the same patient)
MIXED HAMARTOMA
The external (upper) and cut (lower) surfaces of a solitary hepatic mass, 7x5x4 cm, that is a mixed hamartoma with an irregular, granular, pale tan surface are from a 3 month old girl. (Fig. 17 from Benign Epithelial Tumors and Tumor-Like Lesions of the Liver. In: Hepatocellular Carcinoma. Okuda, K. and Peters, R.L. [Eds.]. New York: John Wiley & Sons, 1976.)

the right lobe by a pedicle (Franklin and Downing).

Microscopic. The bulging nodules are a multitude of pseudolobules of varying size composed of masses of hepatocytes surrounded by fibrous tissue. Bile ductular units are present at the margins of the hepatocytes (figs. 20, 21). The bile ductules merge with adjacent hepatocytes and thus appear to arise by hepatocellular metaplasia (fig. 21). The connective tissue is very dense, compact, and contains thick-walled hepatic arteries.

Differential Diagnosis. The distinction of mixed hamartoma from focal nodular hyperplasia is facilitated by its gross appearance. Mixed hamartoma lacks a central scar and is characterized by diffuse uniform nodularity. Microscopic examination of mixed hamartoma reveals abundant diffuse fibrous tissue with numerous bile ductules at the fibrous tissue interface; in focal nodular hyperplasia, islands of bile ductules are present among the hepatic cords, separate from the fibrous strands. Unlike mixed hamartoma, cirrhosis is a diffuse process, not a single mass.

HEPATOCELLULAR ADENOMA

Hepatocellular adenoma is associated with a multiplicity of conditions and etiologic factors and demonstrates a variety of histologic appearances. In addition to the variations included within the spectrum of the usual forms of hepatocellular adenoma, anabolic steroid-related tumors are separately described due to their distinctive histologic appearance, which often resembles hepatocellular carcinoma.

TYPICAL

SYNONYMS AND RELATED TERMS: Benign hepatoma; solitary adenoma.

Definition. Hepatocellular adenoma is a circumscribed, often encapsulated, gray-brown bulging tumor composed of hepatocytes arranged in cords, and occasionally forms bile. The tumor is devoid of portal tracts and terminal hepatic veins. Necrosis, hemorrhage, and rupture are frequent in larger tumors. Although usually solitary, hepatocellular adenoma may be multiple.

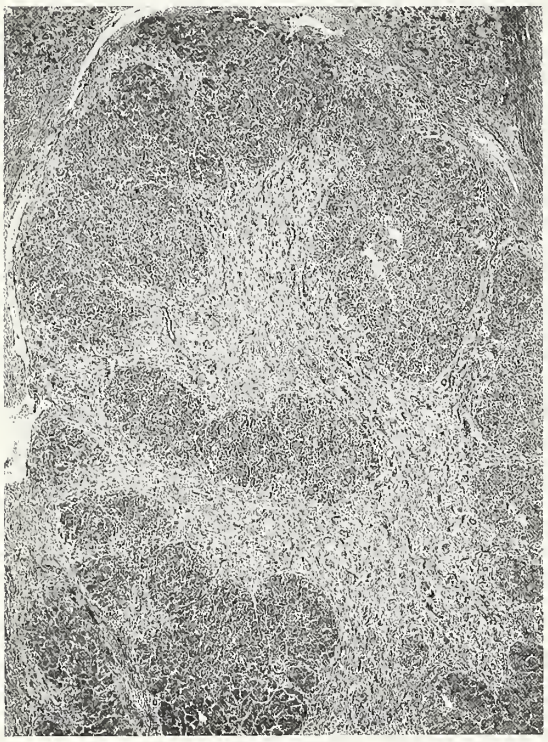


Figure 20
MIXED HAMARTOMA
The mixture of hepatocytes in broad masses are divided by fibrous bands containing bile ductular units. X35.

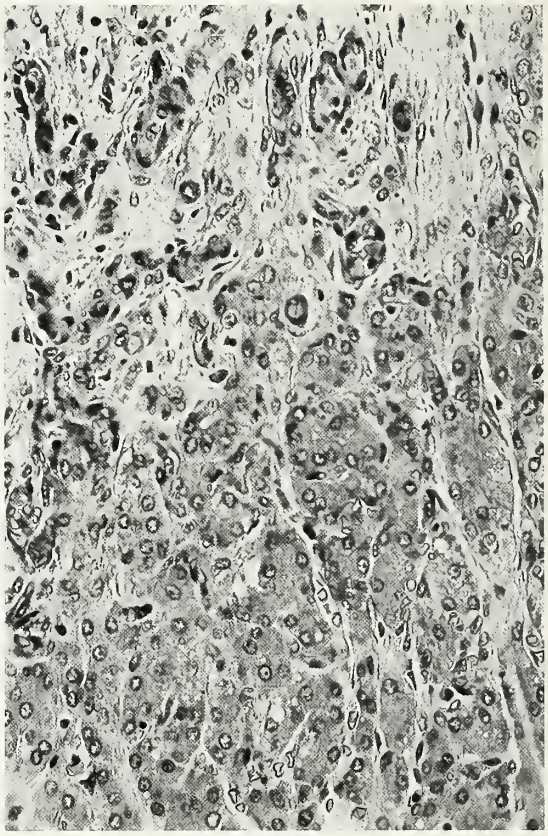


Figure 21
MIXED HAMARTOMA
There is transition of hepatocytes to bile ductular units in mixed hamartoma. X300.

Incidence. The incidence of hepatocellular adenomas varies with its etiology, which is identifiable in the majority of cases. Table 3 lists the etiologic factors and their relative frequency. The majority of hepatocellular adenomas are related to use of oral contraceptives, with an estimated incidence of 3 to 4 per 100,000 users (Rooks et al.).

Type 1. Estrogen-associated Hepatocellular Adenoma

Clinical Features. Because the clinical features are related to the etiologic agent, estrogen-associated hepatocellular adenomas are usually detected in young women with more than 5 years of medication (Edmondson et al., 1976). In our series of 52 consultation patients, the age range was 20 to 50 years, with the average being 31.7 years. Ten of the 52 were over 40 years old. Hepatocellular adenoma has been reported in estrogen users as young as 17 years of age. Clinically, hepatocellular adenoma may present as: (1) a liver mass; (2) abdominal pain (usually right upper quadrant); (3) intra-abdominal hemorrhage with liver tumor rupture; or (4) as an incidental finding. The evaluation of a young woman on estrogen may include

Table 3

HEPATOCELLULAR ADENOMA ETIOLOGIC FACTORS AND INCIDENCE

	Etiologic Factor	Frequency
1.	Estrogen: Female — Birth control pill	Common
	Male — Stilbestrol	Rare
2.	Anabolic steroid hepatocellular adenoma	Common
3.	Metabolic disease hepatocellular adenoma	
	Glycogen storage disease I	Frequent
	Tyrosinemia	Common
4.	Spontaneous hepatocellular adenoma	Rare
5.	Other conditions	
	Familial (including diabetes)	Rare
	Cirrhosis	Rare

radiographic or other studies that reveal a hepatic mass prior to rupture or bleeding. Some hepatocellular adenomas may be discovered during elective surgery.

Pathogenesis. The mechanism by which the more commonly used estrogens, mestranol and ethinyl estradiol, cause hepatocellular proliferation is unknown. The liver metabolizes these compounds, and estrogen-binding receptors have been reported on the hepatocyte membrane and within the cytoplasm. It has been proposed that estrogens bind with membrane receptors and that this complex alters the chromatin, thus changing hepatocyte function by affecting mRNA activity (Dickson and Eisenfeld). Cytoplasmic progesterone receptors, in the absence of estrogen receptors, have also been reported in the hepatocellular adenoma (Carbone and Vecchio). The growth of hepatocellular adenoma may be by amitotic cell division because in many adenomas, the hepatocytes are binucleate and mitoses rare. At the margin of the tumor, transformation of adjoining hepatocytes occur (fig. 22). In encapsulated tumors, this transformation of benign hepatocytes to neohepatocytes occurs outside the capsule. Therefore, transformation of benign hepatocytes is suspected, based on histologic appearance, but remains unproved by other technics.

Withdrawal of the estrogenic compounds results in regression of the hepatocellular adenoma, although the time period may be many months. One patient with multiple hepatocellular adenomas discontinued estrogen use and an autopsy performed 8 years later showed no evidence of adenomatous growth (Edmondson et al., 1977). Progressive enlargement after cessation of estrogen has also been reported (Mariani et al.).

The mechanism of infarction is not well understood, but some blood vessels within the hepatocellular adenoma are thrombosed. Apparently, infarction does not uniformly result in hemorrhage with rupture, as many larger hepatocellular adenomas do have central areas with amorphous connective tissue, hemosiderin, and

scarification, indicative of previous injury and repair. Another vascular alteration is that of peliosis hepatis, which appears only in the hepatocellular adenoma, not in the adjacent normal liver.

Gross. A solitary hepatocellular adenoma is more common and occurred in 39 of our 52 patients. Twenty-six were in the right lobe, 13 in the left, and both lobes were involved in nine patients. The caudate lobe was the site in one patient. Usually hepatocellular adenoma is seen readily from the external surface and was pedunculated in six patients. Glisson's capsule was smooth and glistening in those not ruptured, although there was irregular bulging (fig. 23). The tumor is usually more than 10 cm in diameter. One-quarter of the tumors in our series were smaller than 10 cm, and three of these were ruptured. Tumor weight was over 500 g in 14 of the 47 resected hepatocellular adenomas; the heaviest in our series was 2770 g.

A variegated, irregular, bulging cut surface of tan tissue is noted in those tumors without degenerative change or rupture. This bulging configuration is not the result of septae, but solid hepatocellular growth. Some hepatocellular adenomas have a homogenous texture which is pitted by numerous tiny blood vessels and, rarely, fibrous septae (pl. I-C).

Resected hepatocellular adenomas often show variation in color due to hemorrhage or infarction. The hepatocellular component is lighter tan than the surrounding liver. Both hemorrhage and infarction are obvious if present, although infarction may occur with little or no hemorrhage. Ruptured tumors have abundant hemorrhage, recognized by bright to dark-red clots (figs. 24, 25), and old hemorrhage is dark brown. Degenerative changes, consisting of gelatinous areas or brown-gray connective tissue, and pseudocyst formation are common in

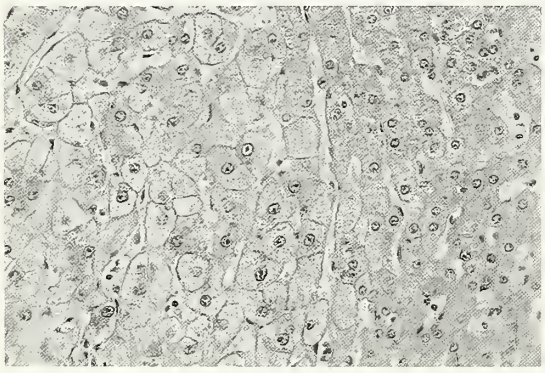


Figure 22
(Figures 22, 29, and Plate I-C
are from the same patient)
HEPATOCELLULAR ADENOMA, Type 1
The transition of the neohepatocytes of the hepatocellular adenoma to normal hepatocytes suggests a transformation, as the cords merge with cells of both types in the same cell plate. X205. (Courtesy of Dr. Seth Haber, Santa Clara, California.)

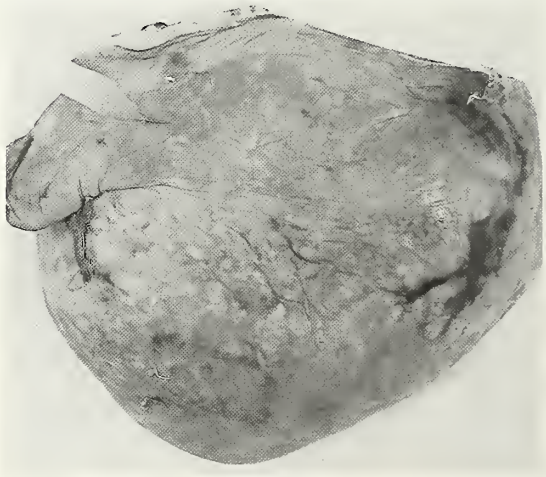
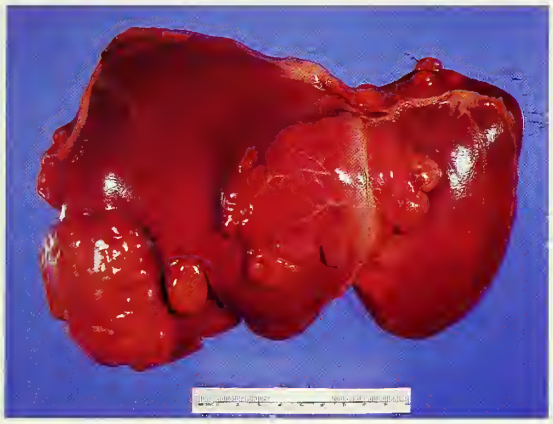


Figure 23
HEPATOCELLULAR ADENOMA, Type 1
Hepatocellular adenoma produced a nodular surface and large abdominal mass (10 cm maximal diameter, 430 g), which was resected in a 25 year old woman on oral contraceptives for 4 years. (Courtesy of Dr. Roy L. Byrnes, Laguna Beach, California.)

PLATE I

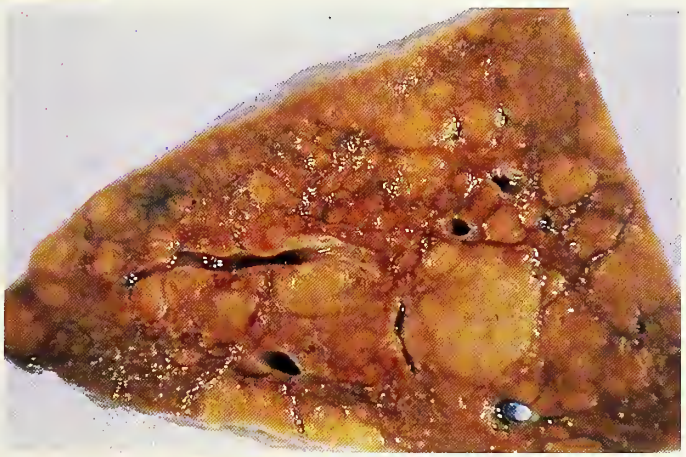


A. MACROREGENERATIVE NODULE

This is the external surface of a liver with large areas of macroregenerative nodules from a patient who died of submassive hepatic necrosis (Fig. 10 from Benign Epithelial Tumors and Tumor-Like Lesions of the Liver. In: Hepatocellular Carcinoma. Okuda, K. and Peters, R.L. [Eds.]. New York: John Wiley & Sons, 1976.)

B. NODULAR REGENERATIVE HYPERPLASIA

This is a gross illustration of the cut surface with bulging, tan nodules, lighter in color than the surrounding, darker liver. The nodules are diffuse and vary in diameter, ranging up to slightly more than 1 cm. No necrosis or hemorrhage is noted. This was an incidental finding in a drowning vitctim. (Courtesy of John N. O'Donnell, Auburn, California.)



C. HEPATOCELLULAR ADENOMA, Type 1

(Plate I-C and figures 22, 29 are from the same patient)

Two of three hepatocellular adenomas (10, 5, and 1 cm in diameter) are noted in the right lobe of this liver. The cut surface has a bulging, bright tan-orange, stippled texture due to many small blood vessels. The 30 year old female patient had a large hepatic mass after using oral contraceptives for 3 years. The right lobe and a portion of the left lobe were resected and 14 years later she was well, without hepatic lesions. (Courtesy of Dr. Seth Haber, Santa Clara, California.)

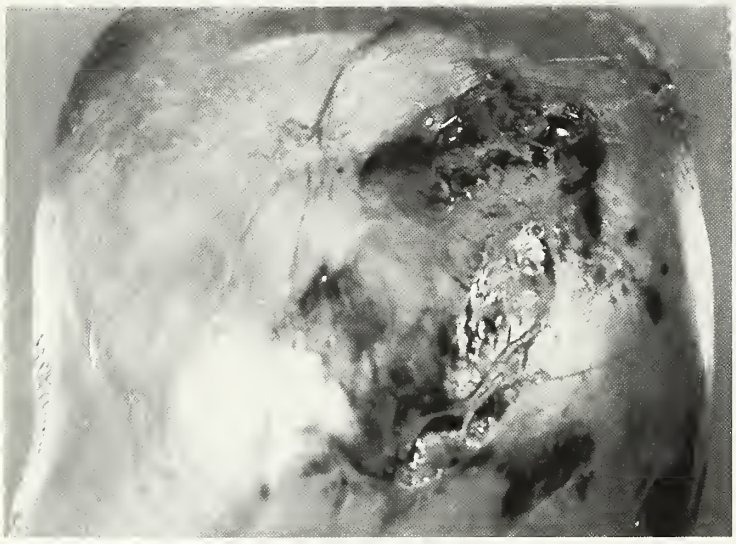


Figure 24
(Figures 24, 25, and 37
are from the same patient)
HEPATOCELLULAR ADENOMA, Type 1
Glisson's capsule is ruptured over a large hepatocellular adenoma that produced intra-abdominal hemorrhage in a 26 year old woman on oral contraceptives. The patient recovered after the 1350 g right lobe was resected. (Courtesy of Dr. Patrick W. Riley, Reno, Nevada.)

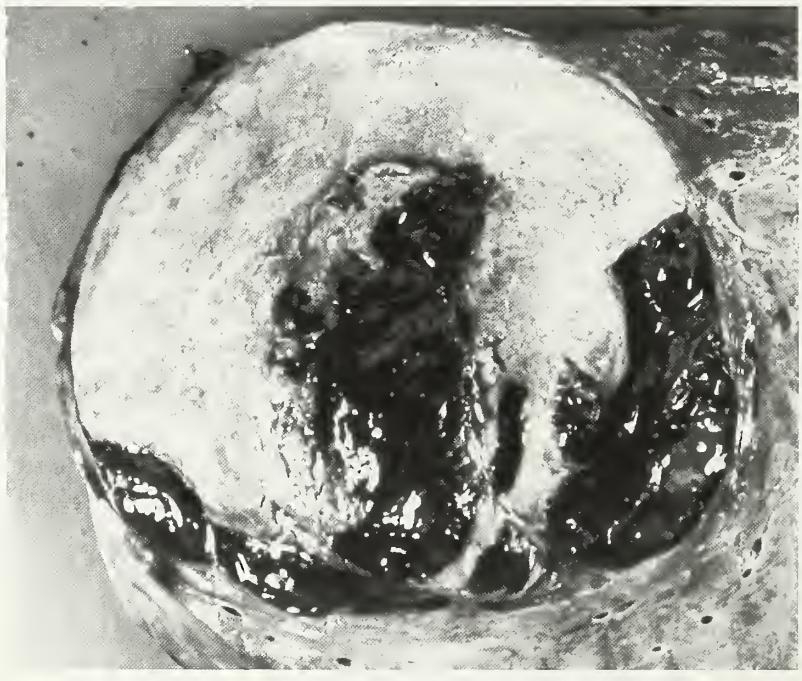


Figure 25
HEPATOCELLULAR ADENOMA, Type 1
The cut surface of the hepatocellular adenoma shown in figure 24 reveals large areas of hemorrhage and infarction. (Courtesy of Dr. Patrick W. Riley, Reno, Nevada.)

larger tumors. Peliosis hepatis is common and may be pronounced, producing many prominent bloody areas (fig. 26).

Microscopic. The hepatocytes within the hepatocellular adenoma look slightly different than those of the adjacent non-neoplastic parenchyma. The neoplastic hepatocytes grow in a discernible cord pattern although in many tumors the cords are closely approximated, and a sheet-like pattern results. Hepatocellular adenomas are composed of four distinctive types of neoplastic hepatocytes that are referred to as neohepatocytes because of their similarity to normal hepatocytes, the absence of malignant cytologic features, and their presence only within the hepatocellular adenoma and not the adjacent normal liver. The common neohepatocyte, occurring in one-third of hepatocellular adenomas associated with estrogen use, resembles a normal hepatocyte (except for its presence within a hepatocellular adenoma) and has acidophilic cytoplasm (fig. 27). A second type of neohepatocyte is "hydropic" and apparently the cellular organelles are concentrated around tiny canaliculi (figs. 28-30). This hydropic type usually grows at the margin of the adenoma or just beneath the capsule, and occurred in one-sixth of the cases in our series. A third type of neohepatocyte is called the pleomorphic type because of its larger size and abnormally large nucleus with dense chromatin. Giant cell formation may occur in approximately 10 percent of hepatocellular adenomas (figs. 31, 32). The overall growth pattern must be observed carefully to exclude malignant change, which is recognized by nodule-within-nodule growth and by the presence of large trabeculae. The fourth type of neohepatocyte has a centrally located nucleus and clear cytoplasm with abundant glycogen.

Cytoplasmic changes of other types may be noted in many hepatocellular adenomas. Alcoholic hyalin may be abundant (fig. 33). Cholestasis is often present, especially in the hydropic type. Fatty hepatocytes are occasionally present and may be prominent in some hepatocellular adenomas. The skeletal framework of hepatocellular adenoma consists of blood vessels and associated connective tissue that is usually scanty, but may form thin septae. Blood vessels are often very prominent at the margins and within the tumor. Although intimal fibrosis is present in capsular vessels, arterial branches within the tumor are free of such intimal thickening. The arteries within the hepatocellular adenoma are closely accompanied by veins (figs. 34, 35). Degenerative changes may be present in the center of the tumor, especially larger hepatocellular adenomas (greater than 10 cm) characterized by necrosis, hemorrhage, densely collagenous scarifications, perivascular edema, and occasionally, angiomatoid vascular ectasia (fig. 36). Wide dilatation of the sinusoids is also common and forms peliosis hepatis (figs. 37-39). A distinctive fibrodegenerative lesion composed of poorly cellular masses of amorphous eosinophilic material within the dilated sinusoids may be observed. The formation of a fibrous capsule occurs at the periphery of most tumors; although thin and incomplete, it is composed of poorly cellular collagenous connective tissue.

Electron microscopic study of hepatocellular adenoma has not disclosed diagnostic features. Intramitochondrial inclusions have been recorded, but are not specific.

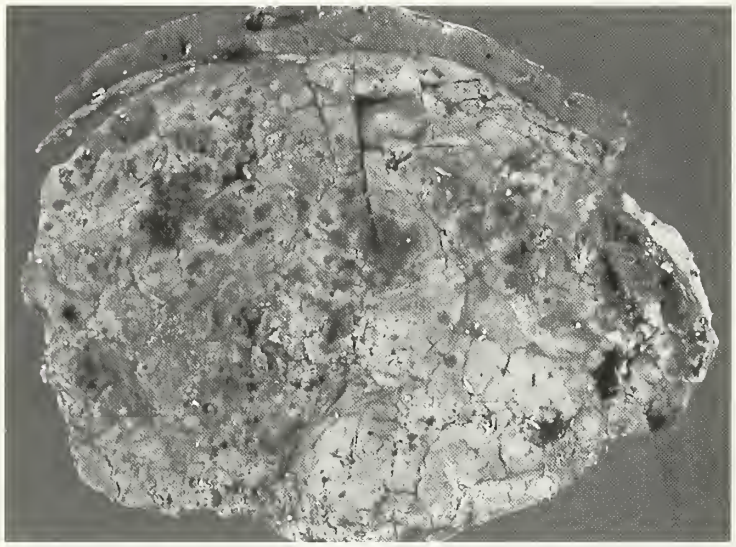


Figure 26
HEPATOCELLULAR ADENOMA, Type 1
This is the cut surface of a large hepatocellular adenoma with extreme peliosis hepatis, old areas of necrosis, and pseudocyst formation in a 33 year old woman who had a palpable abdominal mass and had used oral contraceptives for 9 years. The right lobe was resected. (Courtesy of Dr. Jane Wu, Madison, Wisconsin.)

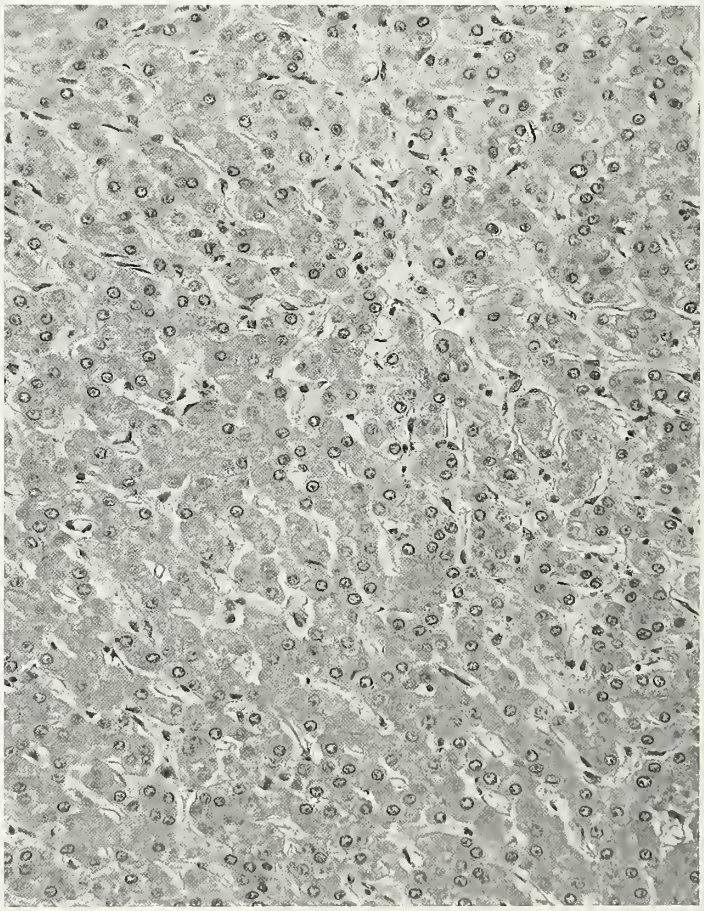


Figure 27
HEPATOCELLULAR ADENOMA, Type 1
This figure shows hepatocellular adenoma with neohepatocytes forming narrowing cords of acidophilic cells in a 33 year old woman on oral contraceptives for 9 years. X125. (Courtesy of Dr. Lawrence K. Hussey, South Bend, Indiana.)

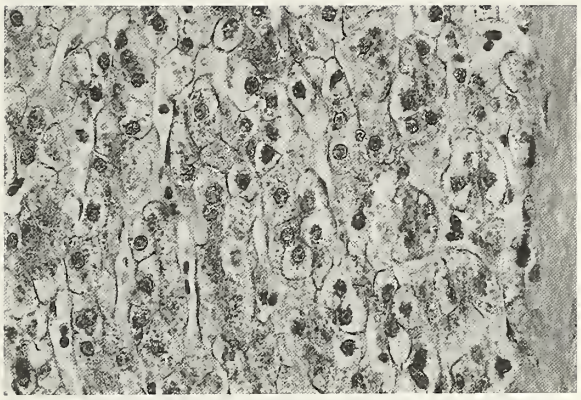


Figure 28
HEPATOCELLULAR ADENOMA, Type 1
This is an example of hepatocellular adenoma with watery vacuolization in neohepatocytes. X240. (Courtesy of Dr. Schuyler Aijian, Arcadia, California.)

Figure 29
(Figures 29, 22, and Plate I-C
are from the same patient)
HEPATOCELLULAR ADENOMA, Type 1
The abundant, clear, vacuolated cytoplasm of the neohepatoctyes in this hepatocellular adenoma obliterates some of the cord pattern. X225. (Courtesy of Dr. Seth Haber, Santa Clara, California.)

Figure 30
HEPATOCELLULAR ADENOMA, Type 1
Many acini contain bile pigment in this hepatocellular adenoma with hydropic neohepatocytes in a 37 year old woman who was on oral contraceptives for 7 years. The tumor ruptured and was resected. X205. (Courtesy Dr. Kamal Ishak, Washington, D.C.)

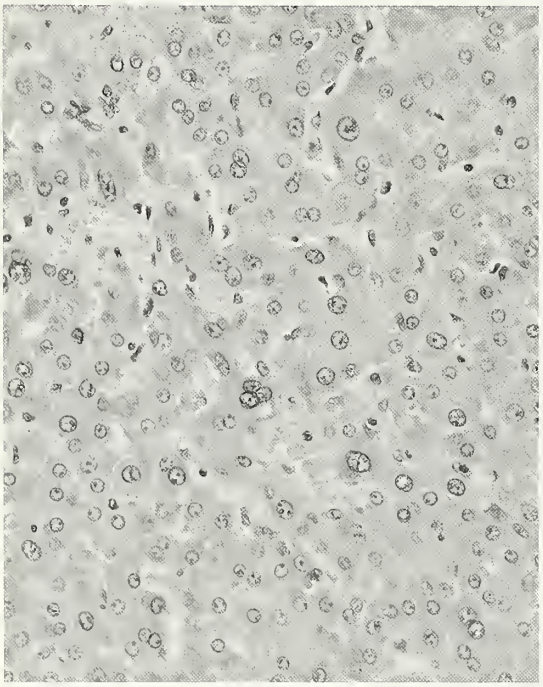


Figure 31
HEPATOCELLULAR ADENOMA, Type 1
This hepatocellular adenoma with rupture from a 28 year old woman demonstrates considerable variation in cell size of the neohepatocytes with some multinucleated giant cells present (see also fig. 32). X190. (Courtesy of Dr. Patrick W. Riley, Reno, Nevada.)

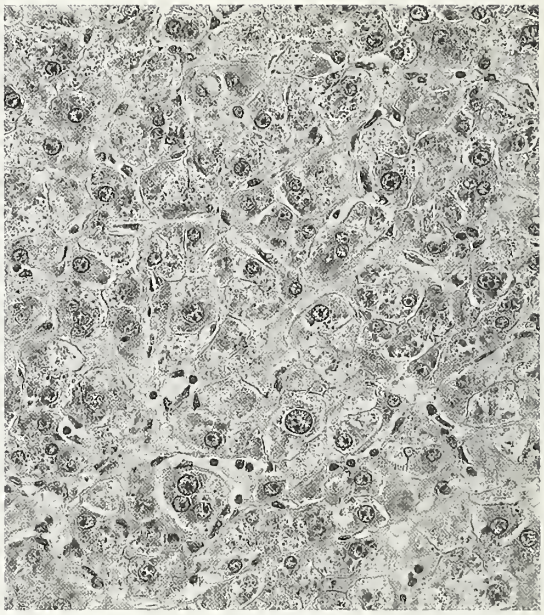


Figure 32
HEPATOCELLULAR ADENOMA, Type 1
Giant cells are prominent in a hepatocellular adenoma of a woman on oral contraceptives for 18 years who had resection and was well 4 years later. X225. (Courtesy of Dr. Karen Cove, Los Angeles, California.)

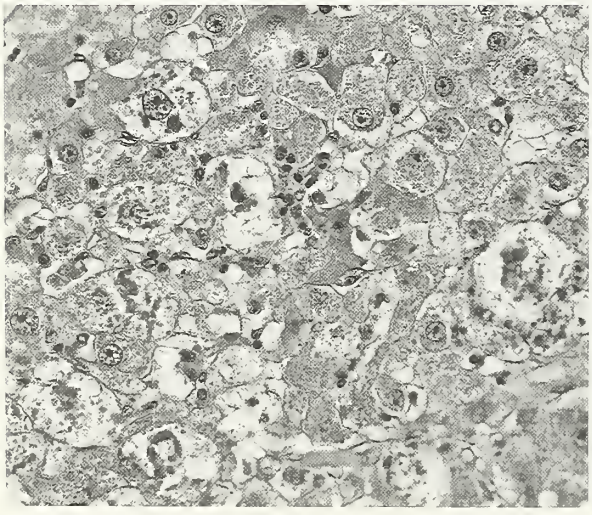


Figure 33
HEPATOCELLULAR ADENOMA, Type 1
Alcoholic hyalin in hydropic neohepatocytes is seen in a hepatocellular adenoma from a 42 year old woman on oral contraceptives for 13 years. A 180 g, 7x6x8 cm mass was resected. X260. (Courtesy of Dr. Mary Contakos, Walnut Creek, California.)

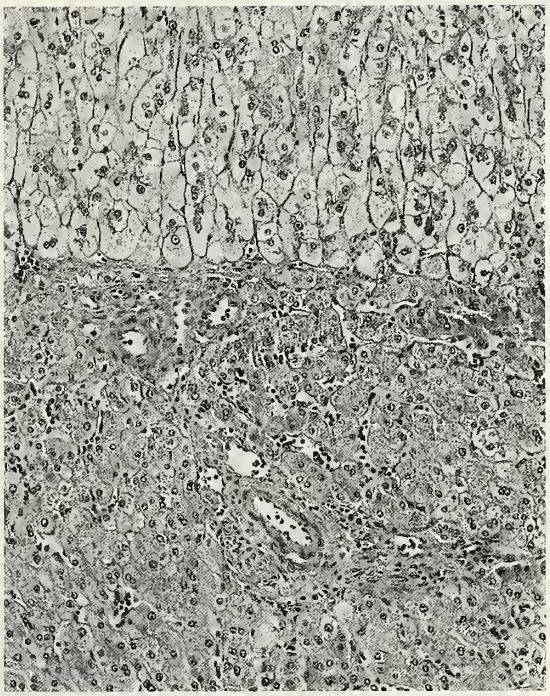


Figure 34
HEPATOCELLULAR ADENOMA, Type 1
In this nonencapsulated hepatocellular adenoma, several afferent arteries arise in the portal tract adjacent to the hepatocellular adenoma. The neohepatocytes have marked watery vacuolization. A 22 year old woman had surgical resection of a ruptured hepatocellular adenoma. Subsequently, a 6 cm in diameter and another 2 cm in diameter hepatocellular adenoma were resected. She was symptom free 7 years after surgery. X70. (Courtesy of Dr. Charles Platz, Iowa City, Iowa.)

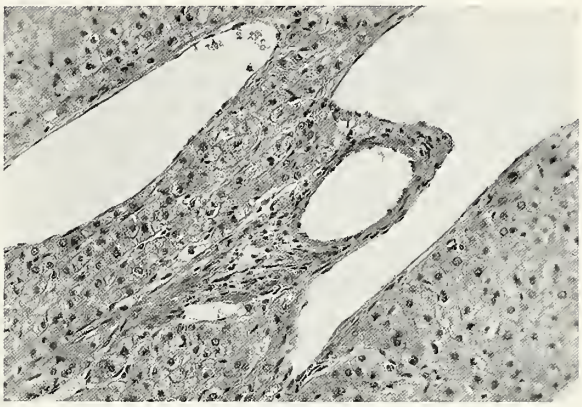


Figure 35
HEPATOCELLULAR ADENOMA, Type 1
A large artery and vein are closely approximated, a common finding in hepatocellular adenoma. This hepatocellular adenoma arose in a 34 year old woman on oral contraceptives for 10 years. The solitary, large (28x22x16 cm) tumor was resected. X150. (Courtesy of Dr. K. Jiyamapa, Toledo, Ohio.)

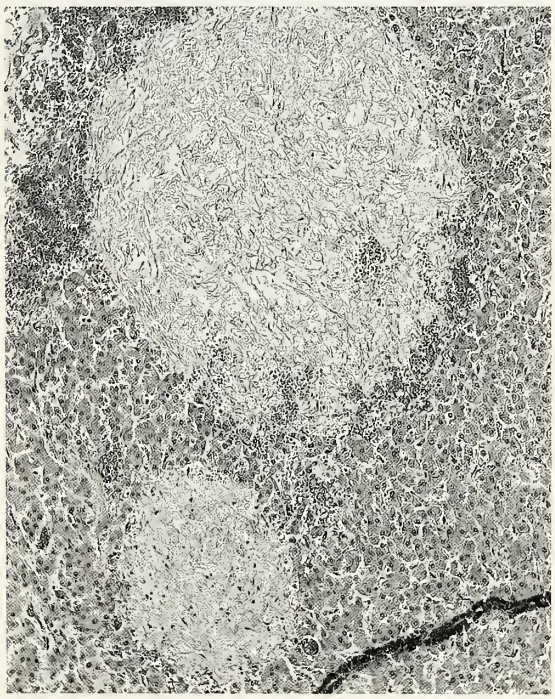


Figure 36
HEPATOCELLULAR ADENOMA, Type 1
A round fibrodegenerative area is in the center of a hepatocellular adenoma with rupture from a 38 year old woman who had taken oral contraceptives for many years. X75. (Courtesy of Dr. Kenneth Crow, Albany, Oregon.)

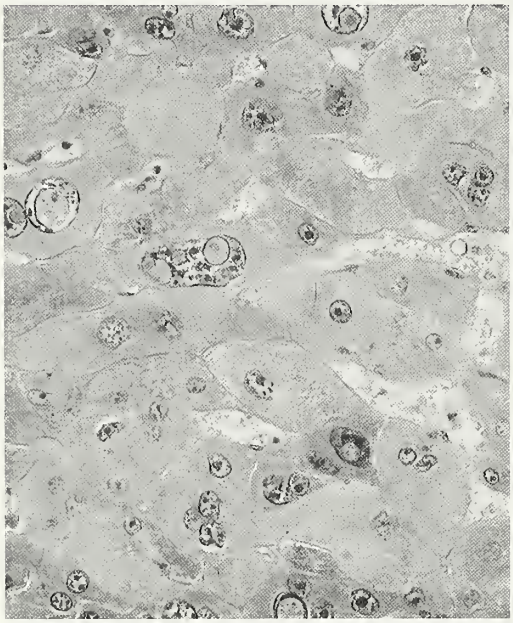


Figure 37
(Figures 37 and 38 are from the same patient)
HEPATOCELLULAR ADENOMA, Type 1

Marked hepatocellular dysplasia is evident in a resected hepatocellular adenoma from a 29 year old woman who had taken oral contraceptives for 3 years and stopped for 2 years before surgery. Two recurrent hepatocellular adenomas were resected 7 years later, and she is alive and well 4 years later. The markedly atypical hepatocytes are noted only in the first large tumor. X530. (Courtesy of Drs. Thomas A. Gaffey, Rochester, Minnesota, and Howard Friedberg, Stanford, California.)

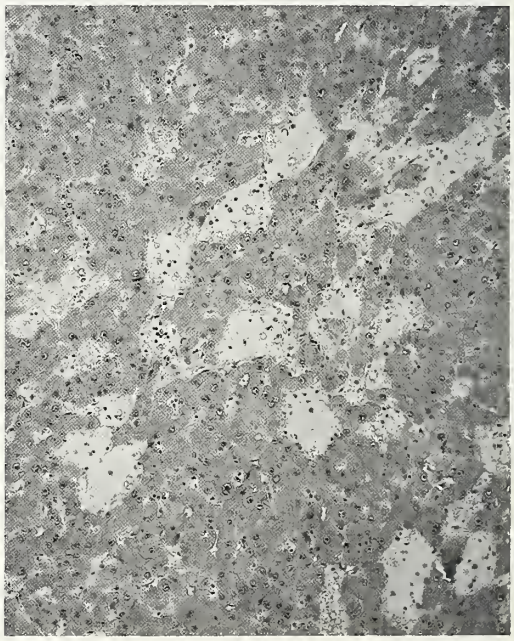


Figure 38
HEPATOCELLULAR ADENOMA, Type 1

The first hepatocellular adenoma resected from the patient in figure 37 shows peliosis hepatis. X125. (Courtesy of Drs. Thomas A. Gaffey, Rochester, Minnesota, and Howard Friedberg, Stanford, California.)

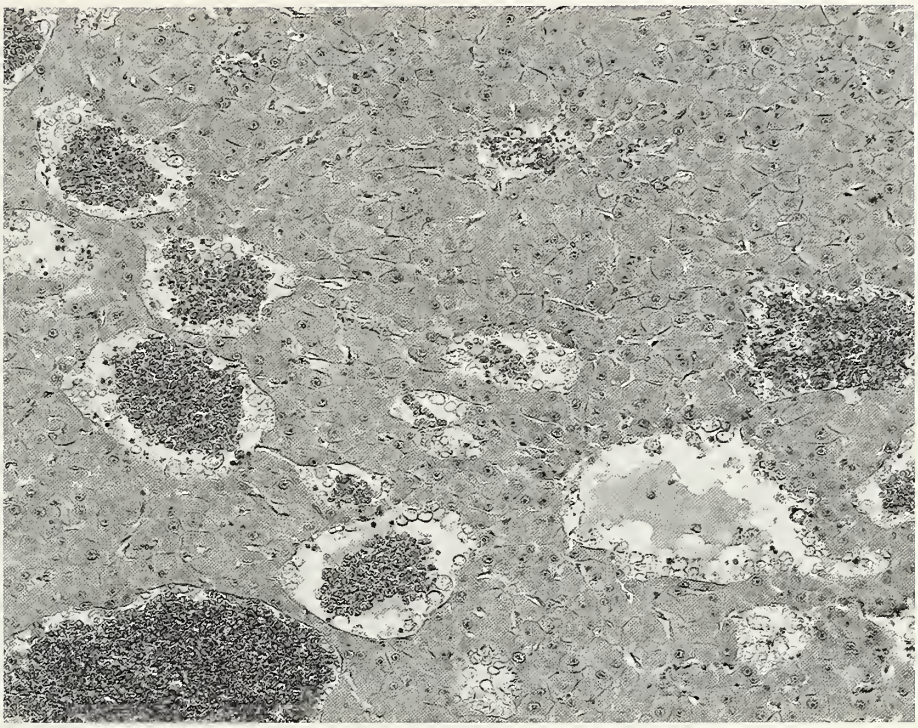


Figure 39
HEPATOCELLULAR ADENOMA, Type 1
Severe peliosis hepatis is seen in this spontaneous hepatocellular adenoma from a 54 year old woman. The 260 g tumor was resected from the left lobe. X110. (Courtesy of Dr. Walter Coulson, Los Angeles, California.)

Type 2. Spontaneous Hepatocellular Adenoma in Women

Clinical Features. These patients usually have an abdominal mass that does not rupture, despite growth to a large size. The majority of hepatocellular adenomas are solitary, although there are few reports of many hepatocellular adenomas in a single liver. We prefer to call this latter condition multiple hepatocellular adenomatosis.

Microscopic. The neohepatocyte types in these hepatocellular adenomas are similar to those present in estrogen-associated tumors. One patient in our series had prominent macrovesicular fatty change (fig. 40) and another large, deeply acidophilic neohepatocytes associated with striking peliosis hepatis.

Type 3. Spontaneous Hepatocellular Adenoma in Men

Clinical Features. These patients are recognized with a large abdominal mass or pain. The age range of our four patients was 22 to 66 years. The tumors were solitary, encapsulated, and ranged in size from 2.5 to 12.5 cm in diameter. Hemorrhage and necrosis were present in three of the four tumors (fig. 41).

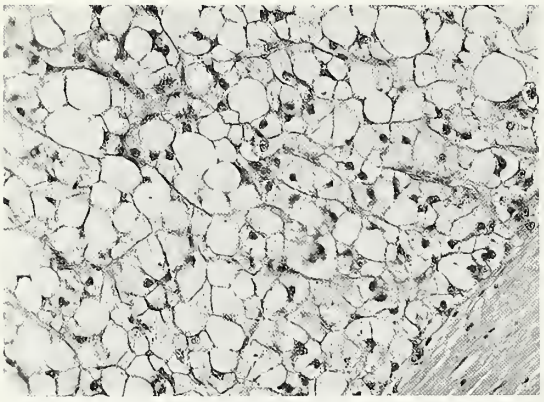


Figure 40
HEPATOCELLULAR ADENOMA, Type 2
Extreme fatty change is noted in neohepatocytes of spontaneous hepatocellular adenoma in a 35 year old woman who noted an abdominal mass for 4 months. X125. (Courtesy of Dr. John Antonius, Portland, Oregon.)

Microscopic. The growth pattern was characterized by nodularity due to fine fibrous septation. In one case, the growth pattern was that of small nodules within larger ones, with associated infarction. In all cases, the neohepatocytes were predominantly acidophilic with fewer hydropic forms. Fatty change was present in two of the four patients. Heavy lipochrome-like pigmentation was present in the hydropic neohepatocytes in one tumor (fig. 42).

Type 4. Spontaneous Hepatocellular Adenoma in Children

Clinical Features. In children, hepatocellular adenomas are rare, less common than focal nodular hyperplasia. Of five patients in our series, four were girls (10 months, 18 months, 30 months, and 12 years of age), and the other was a male infant. The clinical course of unresected spontaneous hepatocellular adenomas may be prolonged, as in two of our patients. One had emergency surgery following abdominal trauma at age 12 and

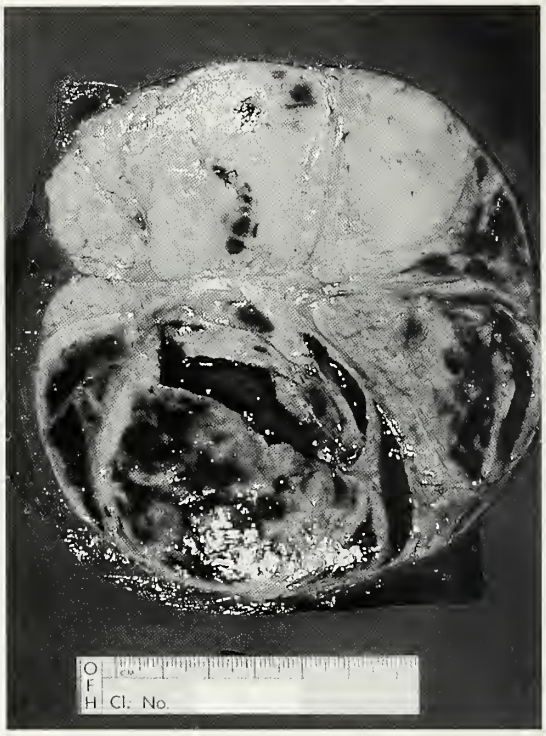


Figure 41
(Figures 41 and 42 are from the same patient)
HEPATOCELLULAR ADENOMA, Type 3
This lobulated hepatocellular adenoma with hemorrhage was diagnosed in a 32 year old man. The first tumor (635 g) was resected in 1967. In 1975, a similar tumor was removed. Eight years later he was free of symptoms. (Courtesy of Dr. William T. Mitchell, Jr., New Orleans, Louisiana.)

multiple hepatocellular adenomas were documented. A ruptured hepatocellular adenoma of the right lobe was removed and a biopsy of another nodule taken. Five years later, surgery for another condition revealed that the liver was unchanged. The second patient had a large hepatic tumor, which was considered hepatocellular carcinoma, biopsied at 1 year of age. The liver grew to such a size that the patient had difficulty walking by age 3 years. At age 19 years, the liver was not palpable and a liver scintiscan was normal, indicating the tumor had regressed.

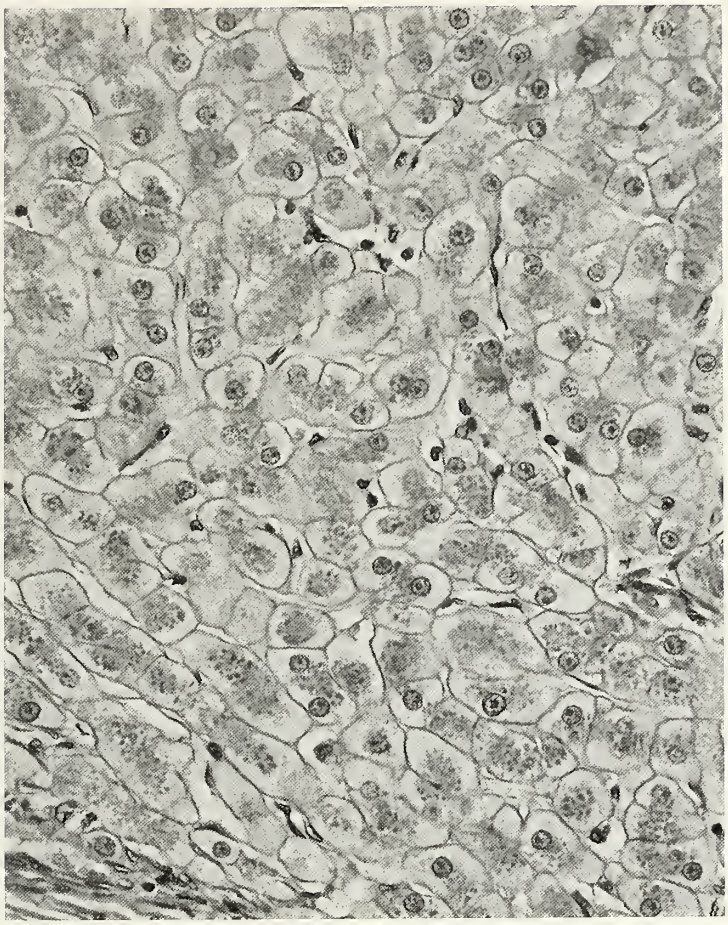


Figure 42
HEPATOCELLULAR ADENOMA, Type 3
This shows the heavy lipochrome-like pigment of neohepatocytes in the hepatocellular adenoma. X360. (Courtesy of Dr. William T. Mitchell, Jr., New Orleans, Louisiana.)

Microscopic. The resected tumors were encapsulated and yellow-tan. The largest tumor was 24 cm in diameter. In three patients, the neohepatocytes were dispersed in sheets with no definite cord pattern. The cells were predominantly acidophilic with a mixture of hydropic forms. In two patients, the cord pattern was well-defined and pericanalicular lipochrome was abundant.

Type 5. Metabolic Disease-associated Hepatocellular Adenoma

Definition. Hepatocellular adenomas arising in the setting of an underlying metabolic disease are benign neoplasms that are histologically identical to the more common estrogen-related hepatocellular adenoma. Metabolic diseases associated with hepatocellular adenoma include glycogen storage disease type I and

tyrosinemia. These hepatocellular adenomas are also associated with development of hepatocellular carcinoma.

Incidence. As of 1986, hepatocellular adenoma arising in glycogen storage disease type Ia was reported in 35 patients (Coire et al.). Because current medical treatment has prolonged the survival of patients with these conditions, increasing numbers of hepatocellular adenomas associated with metabolic diseases are expected.

Clinical Features. Several metabolic disorders predispose to the development of hepatocellular adenoma including glycogen storage disease type Ia, galactosemia, and tyrosinemia. Multiple hepatocellular adenomas develop in the teenage years in as many as 50 percent of glycogen storage disease type Ia patients. Hepatocellular carcinoma may occur later; three reported patients range from 14 to 31 years (Coire et al.; Howell et al.). Dietary therapy promotes regression of glycogen storage disease type Ia-hepatocellular adenoma (Parker et al.). Diabetes mellitus has also been reported to be associated with hepatocellular adenoma in a few patients. Some of their family members also had hepatocellular carcinoma (Foster et al.).

Microscopic. The hepatocellular growth pattern is predominantly acidophilic small cell (common type of neohepatocyte), although macrovesicular fat may predominate in the neohepatocytes (Coire et al.).

Differential Diagnosis of all Types (includes anabolic steroid-related hepatocellular adenoma)

The major difficulty in differential diagnosis is the distinction of normal liver from hepatocellular carcinoma. A needle biopsy may be diagnostic of hepatocellular adenoma if there is a long fragment of hepatocytes devoid of portal areas and having typical prominent vessels; these vessels are not noted in normal liver. An excision of a large portion (or the entire nodule) may be difficult to distinguish from hepatocellular carcinoma and may be classified as borderline hepatocellular carcinoma if diagnostic features of adenoma are not found. Table 4 indicates the major histologic features of hepatocellular adenoma compared to hepatocellular carcinoma. Trabeculae and thick cords are the most helpful features for the identification of hepatocellular carcinoma.

Table 4

HISTOLOGIC CRITERIA OF HEPATOCELLULAR ADENOMA Versus HEPATOCELLULAR CARCINOMA

Criterion	Hepatocellular Adenoma	Hepatocellular Carcinoma
Mitosis	Absent	Present
Cord thickness	2-3 cells maximum	Sheets
Bulging nodule within nodule	Usually absent	Present
Margin	Pushing	Infiltrative
Portal vein invasion	Absent	Often present
Cytologic atypia	Usually absent	Common
Degenerative change	May be distinctive	Absent
Hepatocytes	"Neohepatocytes"	Not neohepatocytes

Tumors arising in cirrhosis are usually easily recognized as hepatocellular carcinoma and not hepatocellular adenoma. We have only one example of hepatocellular adenoma in an autopsy series of 4600 cirrhotic livers. Distinction between a single macroregenerative nodule in a cirrhotic liver and hepatocellular adenoma or well-differentiated hepatocellular carcinoma may be very difficult on gross examination alone. The presence of portal areas within the nodule identifies macroregenerative nodule. Nodule-within-nodule growth and cellular atypia (variation in nuclear size and shape), acinar formation, and mitosis are features helpful for recognition of hepatocellular carcinoma. At the periphery, hepatocellular carcinoma usually infiltrates the sinusoids as individual cells rather than having a broad "pushing border". Furthermore, hepatocellular carcinoma arising in a noncirrhotic liver lacks encapsulation and a thin fibrous rim is often present at some margin of hepatocellular adenoma. The presence of a fibrinodegenerative lesion is a helpful feature of hepatocellular adenoma. However, a moderate degree of cellular atypia occurs in some estrogen-related hepatocellular adenoma, indicating that nuclear features alone are not sufficient to classify the lesion.

Anabolic steroid-associated hepatocellular adenomas often have atypical hepatocellular carcinoma-like features and are discussed in the following section. These anabolic steroid-associated hepatocellular adenomas have a nodule-within-nodule growth pattern as well as acinar formation, which on morphologic grounds alone, may best be considered hepatocellular carcinoma.

Nodular regenerative hyperplasia is another condition that has some features similar to hepatocellular adenoma. Although small areas may resemble hepatocellular adenoma, nodular regenerative hyperplasia is characterized by diffuse involvement of the entire liver by small nodules, whereas hepatocellular adenoma is solitary. In multiple hepatocellular adenomatosis, the nodules are large, several centimeters in size, rather than only a lobule in diameter as in nodular regenerative hyperplasia.

Prognosis of all Types

The prognosis of hepatocellular adenoma is related to the underlying etiologic factor and associated clinical presentation. For those patients with estrogen-related hepatocellular adenoma, cessation of the hormone administration usually results in regression of the tumor, although this may require many months. Furthermore, persistence of a filling defect or enlargement after cessation has been reported (Mariani et al.). A few examples of hepatocellular carcinoma arising in hepatocellular adenoma are known, and we have four examples in our series. In patients with an underlying metabolic disease, conversion of hepatocellular adenoma to hepatocellular carcinoma has been reported in 4 of 36 patients as of 1986. This has stimulated interest in liver transplantation as a means of prevention (Zitelli et al.). Recurrence of hepatocellular adenoma seems more common in spontaneous hepatocellular adenoma than those associated with oral contraceptives and, therefore, follow-up of hepatocellular adenoma varies according to the underlying associated factors.

ANABOLIC STEROID-ASSOCIATED HEPATOCELLULAR ADENOMA

Definition. Anabolic steroid-associated hepatocellular adenoma is a benign hepatocellular proliferation that is usually solitary, occasionally multiple, and regresses upon cessation of anabolic steroid administration.

Incidence. The association of anabolic steroid medication and hepatocellular adenoma was first reported in 1965 and with increasing recognition, 33 patients had been reported by 1981, and an additional 13 patients by 1985.

Clinical. Males predominate, comprising approximately 75 percent of the reported cases, partly because the medication is often provided for hypogonadism. Although ranging from 5 to 68 years of age, most are young and typically present in the adolescent years. In addition to hypogonadism, other indications for anabolic steroid treatment have included: Fanconi's anemia (Johnson et al.); aplastic anemia; impotence; paroxysmal nocturnal hemoglobinuria (Hernandez-Nieto et al.); chronic renal failure with hemodialysis; renal transplantation with anemia; and more recently, athletic body building. Hepatomegaly, abdominal pain, and occasionally, hemoperitoneum due to rupture are the most frequent presenting manifestations (Westaby et al., 1983). The average duration of exposure to steroids prior to recognition of the tumor is 40 to 80 months depending on the underlying condition; patients with Fanconi's anemia frequently develop clinical signs earlier (Carrasco et al.). Although abnormal liver scans may be noted by 12 months following onset of therapy, these changes may not reflect the development of hepatocellular adenomas (Westaby et al., 1977). Elevation of serum α-fetoprotein is not observed in anabolic steroid-associated hepatocellular adenoma, but does occur in anabolic steroid-associated cholangiocarcinoma-hepatocellular carcinoma (Overly et al.).

Pathogenesis. Of the types of anabolic steroids, it is the C-17 alkylated form that appears to be related to the development of neoplastic hepatocellular proliferation (Turani et al.; Zevin et al.). Peliosis hepatis may likely be a common precursor, since peliosis more frequently occurs earlier than anabolic steroid-associated hepatocellular adenoma (Turani et al.) and is often observed within the neoplasm and adjacent nonneoplastic hepatic parenchyma (Shapiro et al.). The pathogenesis of peliosis hepatis may be related to the cytotoxic effect of the anabolic steroids on endothelial cells with subsequent sinusoidal dilatation (Kosek and Smith).

The mechanism of anabolic steroid-induced hepatocellular proliferation is unclear, but might be related to epithelial regeneration following the preceding phase of peliotic "injury". However, peliosis hepatis is not a necessary precursor of hepatocellular adenoma. After 3 months of anabolic steroid treatment, Sweeney and Evans observed diffuse hepatic hyperplasia and generalized nodular hepatocellular hyperplasia in two patients. Peliosis hepatis was not documented in either patient, suggesting that hepatocellular stimulation may be a direct phenomenon.

Many patients with chronic anemia who are on anabolic steroids may develop cirrhosis as a complication of multiple blood transfusions. Thus, hepatocellular carcinoma arising in such a setting may be a

complication of cirrhosis and not anabolic steroid medication.

Gross. Approximately half the patients present with a solitary tumor, the remainder with multiple tumors or more numerous smaller nodules (Ishak). A large tumor (several cm in diameter) may be hemorrhagic (fig. 43) and surrounded by satellite nodules, each a few centimeters in diameter. The size range in one series (Chandra et al.) was 0.3 to 11 cm, the majority being in the 1 to 2 cm range. The nodules are well-circumscribed, tan, yellow, or green (due to bile), and are a different color than

Figure 43
ANABOLIC STEROID-ASSOCIATED HEPATOCELLULAR ADENOMA
This is a cut surface of a large, hemorrhagic spherical anabolic steroid-associated hepatocellular adenoma (9 cm in diameter) in the right upper lobe of a patient with Fanconi's anemia who was on methyl testosterone for 4 years. The mass was dark green and composed of multiple smaller nodules 1 cm in diameter. The remaining liver had numerous small nodules 1 to 5 mm in diameter.

the adjacent nonneoplastic liver. In some cases, the nodules are hemorrhagic and the uninvolved liver may contain bloody foci due to the presence of peliosis hepatis (Shapiro et al.). Sale and Lerner reported a patient with over 100 nonencapsulated hepatic nodules 0.1 to 0.5 cm in diameter.

Microscopic. Marked variation of histologic features is a hallmark of these tumors. Some nodules may be comprised entirely of obviously benign hepatocytes arranged in thin cords (fig. 44). Others contain larger cells with hyperchromatic nuclei and giant cells. Acinus or large follicle formation with central cholestasis is typical (figs. 45, 46). Some tumors may be composed entirely of multinucleated giant cells and are difficult to distinguish from carcinoma (fig. 47). In large tumors, areas of hemorrhage and infarction occur similar to that observed in estrogen-related hepatocellular adenomas. Peliosis hepatis is often present in the adjacent nonneoplastic liver.

Differential Diagnosis. Anabolic steroid-associated hepatocellular adenoma is most readily confused with hepatocellular carcinoma because of the cytologic atypia present in both. Attention to the nuclear/cytoplasmic ratio separates most of the tumors; anabolic steroid-associated hepatocellular adenomas have

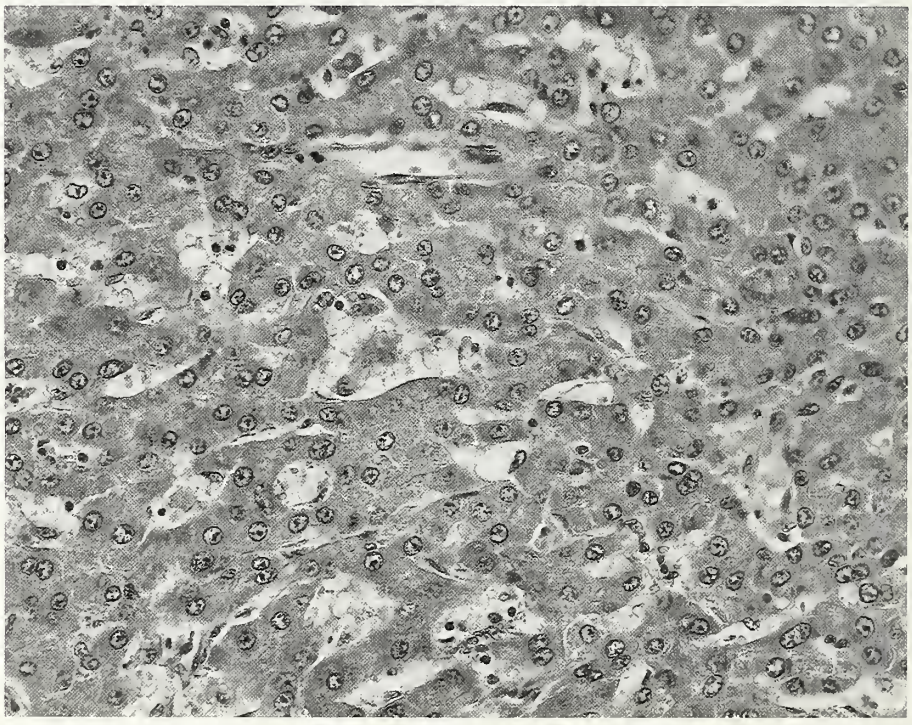


Figure 44
ANABOLIC STEROID-ASSOCIATED HEPATOCELLULAR ADENOMA
This anabolic steroid-associated hepatocellular adenoma composed of slender cords of acidophilic neohepatocytes was seen in a 29 year old man who had taken anabolic steroids for 2 years due to aplastic anemia. He developed two large hepatic nodules that were resected. X260. (Courtesy of Dr. David Strayer, San Diego, California.)

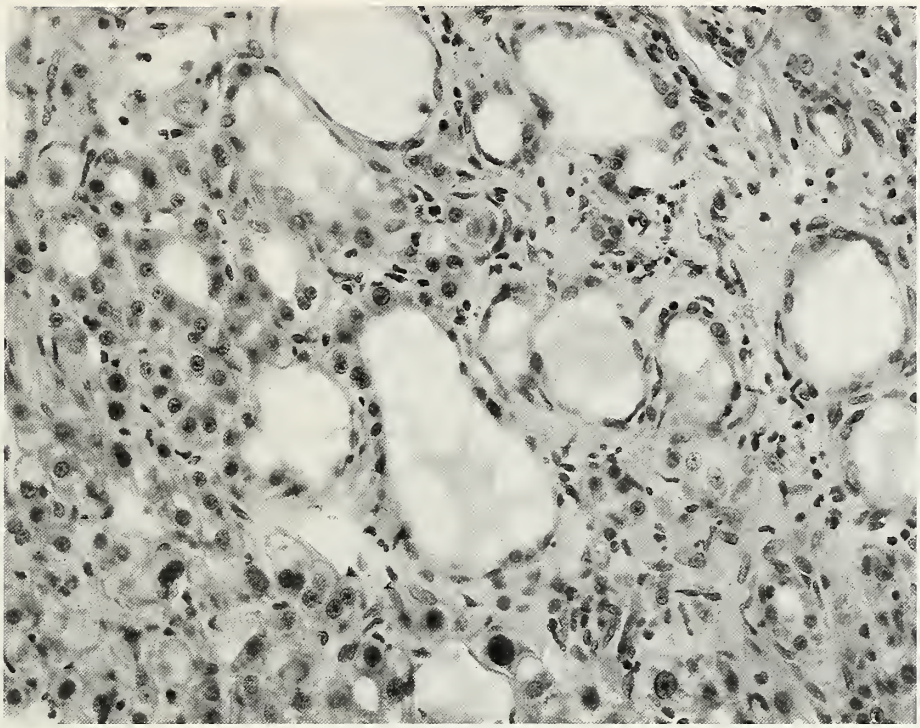


Figure 45
ANABOLIC STEROID-ASSOCIATED HEPATOCELLULAR ADENOMA

This is an anabolic steroid-associated hepatocellular adenoma diagnosed in a 43 year old man who was on testosterone for 16 years due to undescended testicles. The liver was very enlarged and a 10 cm in diameter nodule was resected. He was given 5-fluorouracil and remained well 12 years later. The microscopic pattern includes large follicular pattern with considerable atypia of neohepatocytes. X275. (Courtesy of Dr. Wallace Rindskoff, Des Moines, Iowa.)

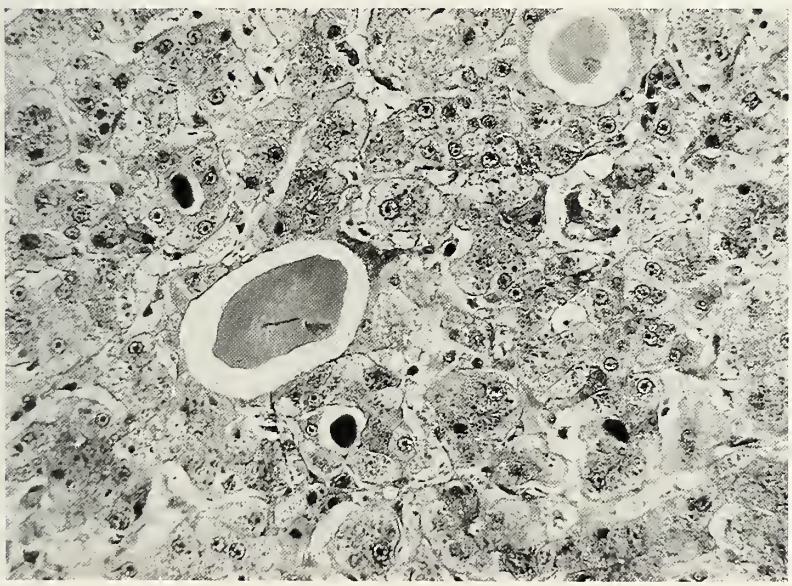


Figure 46
ANABOLIC STEROID-ASSOCIATED HEPATOCELLULAR ADENOMA

This is a mixed acinar and follicular pattern in anabolic steroid-associated hepatocellular adenoma seen in a 5 year old girl who was on oxymetholone for 46 months for aplastic anemia. Eleven months after the steroid was discontinued, the liver scan revealed no evidence of tumor. X250. (Courtesy of Dr. F.L. Johnson, Seattle, Washington.)

Figure 47
ANABOLIC STEROID-ASSOCIATED HEPATOCELLULAR ADENOMA
Many multinucleated giant cells are present in this anabolic steroid-associated hepatocellular adenoma in a 14 year old boy with Fanconi's anemia treated for 5 years with anabolic steroids. X200. (Courtesy of Dr. Boris Ruebner, Davis, California.)

a low ratio and hepatocellular carcinomas have larger nuclei and a higher ratio. However, many anabolic steroid tumors have been reported as hepatocellular carcinoma. Since the metastatic potential in such cases remains unproved, we believe these tumors should be designated adenomas, atypical features notwithstanding. One case of a weight lifter on anabolic steroids demonstrated metastatic, poorly differentiated carcinoma, which was considered hepatocellular in origin (Overly et al.). However, the histologic material was not convincingly hepatocellular carcinoma, although it did contain cholangiocarcinoma. We believe this case is not representative of the numerous anabolic steroid-related hepatocellular tumors reported.

Prognosis. Regression of anabolic steroid-associated hepatocellular adenoma has been repeatedly observed following cessation of the steroid therapy. Furthermore, long-term (10 and 14 years) survival with tumor is documented (McCaughan et al.). Some tumors have not regressed off medication, but metastases have not been documented. In one patient, most of the liver was replaced by a solitary large tumor that persisted 20 months after discontinuation of the anabolic steroid, but no metastases developed (Zevin et al.).

Prognosis is related to the underlying disease for which treatment was indicated (e.g., renal failure or severe anemia), although an occasional patient may succumb to rupture of a large tumor.

MULTIPLE HEPATOCELLULAR ADENOMATOSIS

SYNONYMS AND RELATED TERMS: Many terms employed in the literature are not synonymous with this entity, but generally refer to nodular regenerative hyperplasia, which is distinguished by the smaller size of the hepatocellular nodules.

Definition. Multiple hepatocellular adenomatosis is characterized by the presence of numerous hepatocellular adenomas (usually more than four), typically present in both lobes.

Incidence. Few well-documented case reports are available (Chen and Bocian; Lui et al.), although in some series of hepatocellular adenoma, as many as 10 percent of patients have multiple lesions. Many reported cases of multiple hepatocellular adenoma contain only two or three lesions and therefore would not qualify as multiple hepatocellular adenoma by our definition.

Clinical. Well-documented examples of multiple hepatocellular adenomatosis include that of a 39 year old female with no previous history of oral contraceptive use and the sudden death of a 28 year old woman with a known cardiovascular anomaly. The second patient had biopsy-proven hepatocellular adenoma at age 12 years (12 cm in diameter). At autopsy 16 years later, 10 tumors were present; nine hepatocellular adenomas and one focal nodular hyperplasia (Chen and Bocian).

Pathogenesis. Vascular anomalies have been associated with proliferative hepatocellular activity in partial nodular transformation (Wanless et al., 1985a). Thus, in the report by Chen and Bocian, the long-standing history of pulmonary hypertension, interventricular septal defect, and patent ductus arteriosus may have contributed to abnormal hepatic blood flow.

Pathology. The gross pathology is striking, with multiple bulging nodules up to 5 cm in diameter and prominent surface vascularity (pl. II-A). The nodules are circumscribed but not encapsulated, and the cut surfaces are uniform and pale yellow in contrast to the normal brown liver (figs. 48, 49). The microscopic appearance is that of bland hepatocytes arranged in nodules that compress the adjacent normal parenchyma. Mild fatty change was noted by Lui and associates.

Differential Diagnosis. Nodular regenerative hyperplasia, although histologically similar, consists of nodules less than 1 cm in diameter comprised of individual expanded lobular units. Hepatocellular carcinoma is distinguished by the presence of dysplastic cells, nodule-in-nodule growth, trabeculae several cells in thickness, portal vein invasion, and usually grows as a dominant mass with satellite nodules. Some proported examples of multiple hepatocellular adenomatosis with follow-up are well-differentiated hepatocellular carcinoma as metastasis occurred. In those cases, the nodules blended into the adjacent parenchyma without definite compressive growth, and adjacent satellite nodules were composed of broad trabeculae rather than delicate cell plates. Therefore, the presence of thin cell plates (one and two hepatocytes in thickness) is an important criterion for benign multiple hepatocellular adenomatosis.

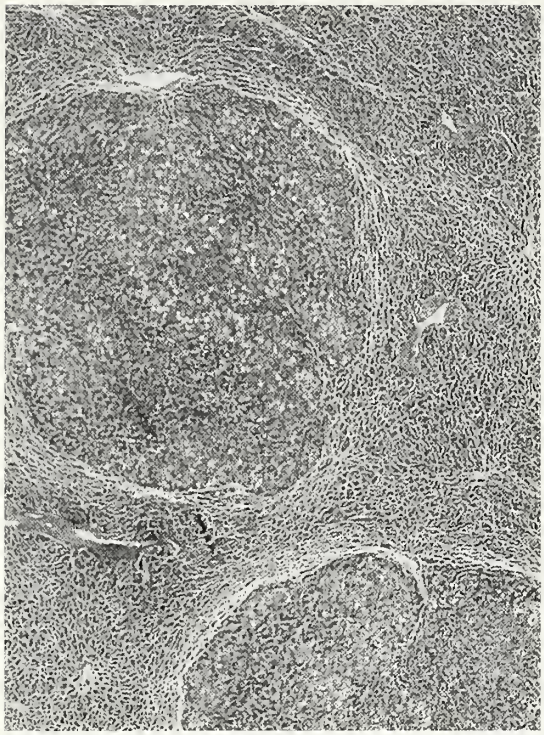


Figure 48
(Figures 48, 49, and Plate II-A are from the same patient)
MULTIPLE HEPATOCELLULAR ADENOMATOSIS
This multiple hepatocellular adenoma has multiple bulging nodules of bland hepatocytes with cords that are uniformly thin and hepatocytes lacking significant nuclear changes. The adjacent liver tissue has a "compressed" appearance due to the growth of the bulging hepatocellular adenoma. X60. (Courtesy of Dr. Al Lui, Torrance, California.)

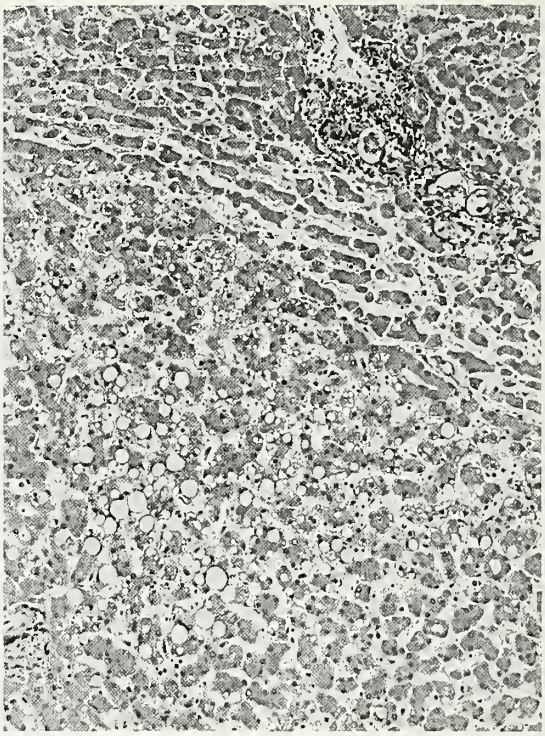


Figure 49
MULTIPLE HEPATOCELLULAR ADENOMATOSIS
A higher magnification shows a single nodule that is well-demarcated from adjacent normal liver. X310. (Courtesy of Dr. Al Lui, Torrance, California.)

HEPATIC CYSTS

The classification of hepatic cysts has remained confusing because of varying criteria and incomplete histologic evaluation (often the result of limited material). Hepatic cysts may be classified as parasitic, congenital or developmental, and acquired. Although other causes of hepatic cystic-like lesions as determined by clinical and radiographic examination include healing abscess, necrotic tumor (both benign hepatocellular adenoma with hemorrhage as well as hepatocellular carinoma), and post-traumatic cyst, each of these lack a true epithelial lining and would more appropriately qualify as pseudocysts. Many reported series of hepatic cysts have been based on clinical and radiographic findings and limited pathologic examination. Review of some of these published series indicated that some solitary hepatic cysts were hepatobiliary cystadenomas. Thus, due to sampling restrictions and differences in classification, the etiology and classification of

the reported cysts are not easily compared and tabulated. The ideal cyst description should include the number of cysts (single vs. multiple, unilocular vs. multilocular), type of epithelial lining (e.g., cuboidal, squamous, mesothelial, ciliated columnar), the presence of stroma (hepatobiliary cystadenoma with mesenchymal stroma), the nature of the fluid content (e.g., mucinous, serous, bile stained, bloody), and the condition of the adjacent noncystic hepatic parenchyma (e.g., presence of von Meyenberg complexes, biliary strictures). Often, developmental or congenital hepatic abnormalities may be clinically inapparent and examination of noncystic hepatic parenchyma is essential. Classification is further complicated by occasional reports of malignant transformation in which extensive tumor necrosis precludes adequate traceability to the underlying abnormality. The various cystic conditions are often incompletely expressed morphologically and may involve only part of the liver, and thus exact classification is difficult. The term "nonparasitic" cyst applies to the entire group of developmental anomalies, excluding hepatobiliary cystadenoma. Table 5 lists hepatic cysts and the key diagnostic components.

SIMPLE HEPATIC CYSTS

SYNONYMS AND RELATED TERMS: Nonparasitic hepatic cyst.

Definition. A simple hepatic cyst is unilocular, usually single, but occasionally multiple (less than 10 cysts), and is usually lined by a simple layer of cuboidal epithelium or, less commonly, squamous or columnar epithelium. The wall is poorly cellular fibrous tissue. The adjacent liver is normal, without fibrosis or von Meyenberg complexes.

Incidence. Simple hepatic cysts are relatively uncommon at autopsy and seem to occur in fewer than 1 percent of routine autopsies in the large LACUSC-MC autopsy series. However, Karhunen and colleagues reported an incidence of 14 percent in 95 consecutive medicolegal autopsies performed on males ranging

Table 5

HEPATOBILIARY CYSTS

Type	Histologic Feature
1. Parasitic	Fibrous wall and organism Echinococcus species
2. Developmental	
A. Solitary (nonparasitic)	Simple epithelial lining, mesothelial, cuboidal, squamous
B. von Meyenberg complex (VMC)	Mixture of fibrous tissue and small ectatic ducts
C. Congenital hepatic fibrosis	Abundant VMC with intervening fibrosis
D. Polycystic liver disease	Large (more than 1 cm) cysts with VMC
E. Choledochal cyst (intrahepatic type)	Dilated major bile duct within liver
3. Undetermined origin	
A. Hepatobiliary cystadenoma in women	Bile duct epithelium with mesenchymal stroma
B. Hepatobiliary cystadenoma in men	Bile duct epithelium without mesenchymal stroma, eosinophilic epithelium

from 35 to 69 years of age. These patients were subjected to thorough examination of the liver, which was sectioned at 1 to 2 cm intervals. Thus, careful examination reveals more cysts than are routinely identified. On the other hand, in living patients, a large surgical series of 150 patients with hepatic cysts was reported (Sanfelippo et al.).

Clinical. Simple hepatic cysts occur more commonly in women (4-5:1), usually as an incidental finding. Approximately 20 percent of the large surgical series reported by Sanfelippo and associates presented with pain, jaundice, hepatomegaly, or intra-abdominal mass. An occasional cyst may become large, up to 20 cm, and careful pathologic examination of multiple areas is essential for proper classification and to exclude multilocular hepatobiliary cystadenoma. Partial excision of simple hepatic cysts may result in recurrence unless adequate drainage is provided.

Pathogenesis. The superficial location of many of these cysts suggests a mesothelial origin, with which clear fluid content would be consistent. Little data is available regarding the presence of bile components in the cystic fluid. The lack of blood or hemosiderin mitigates against a traumatic origin. Liver infarction, drug abuse, and carbon tetrachloride exposure have been related to hepatic cysts (Karhunen et al.).

Pathology. The typical simple hepatic cyst is a bulging cyst beneath the surface of the liver, although some occur deep, inconsistent with origin from surface mesothelium. The wall is 1 mm or less in thickness and the lining consists of a simple layer of cuboidal to low columnar nonciliated epithelium (figs. 50, 51). Significant fibrosis or von Meyenberg complexes are not observed in uninvolved parenchyma.

Differential Diagnosis. Parasitic cysts are distinguished by the presence of a thick, fibrous, often calcified wall and identifiable remnants of a specific organism (usually Echinococcus species). Healing hepatic abscesses lack an epithelial lining and are associated with abundant macrophages and inflammatory cells, as well as microorganisms in some instances. Posttraumatic cysts may be similar to healing abscesses, but hemosiderin deposition is usually prominent.

HEPATOBILIARY CYSTADENOMA

SYNONYMS AND RELATED TERMS: Biliary cyst; biliary cystadenoma; multilocular cystadenoma; bile duct cystadenoma; mucinous cystadenoma.

Hepatobiliary cystadenoma is a relatively rare tumor with three distinctive clinicopathologic patterns. Although these lesions have been called biliary cystadenomas, it is not proved that they are derived from biliary epithelium. For this

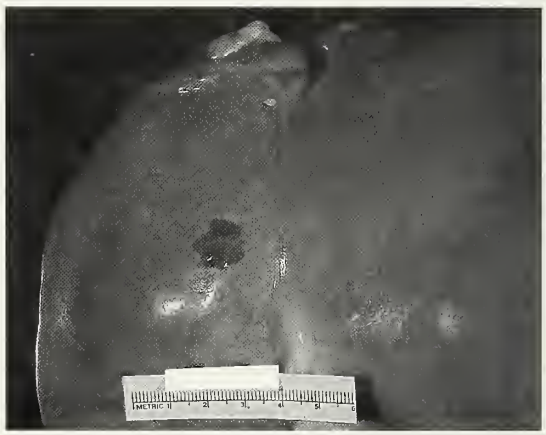


Figure 50
SIMPLE HEPATIC CYST
This shows a simple hepatic cyst, approximately 1 to 1.5 cm in diameter, on the surface of a liver in a 56 year old woman who died of breast cancer.

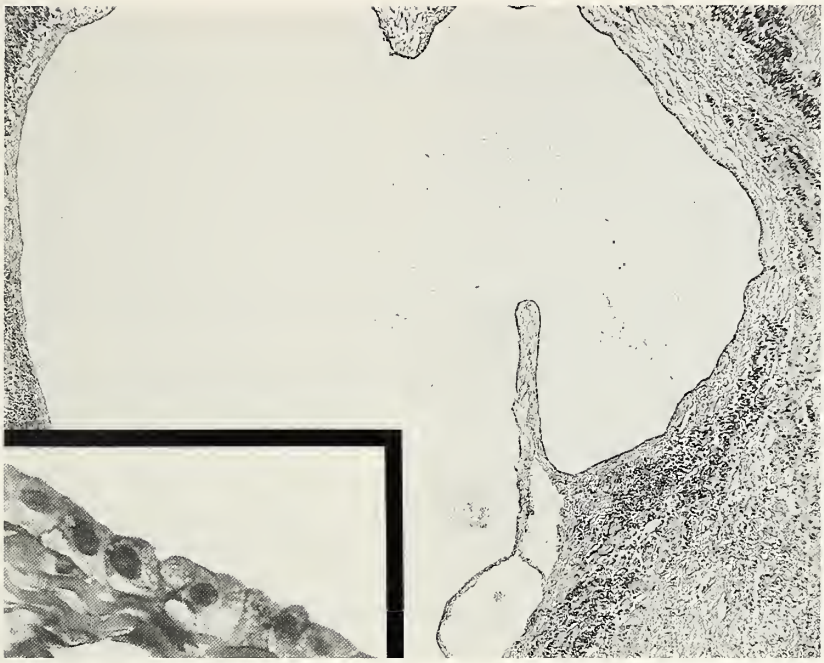


Figure 51
SIMPLE HEPATIC CYST
This is a simple hepatic cyst with a thin collagen layer around the cuboidal epithelial lining. Occasionally, a thin fibrous trabecula may extend into the center. X40. Inset X585.

reason we prefer the less specific designation "hepatobiliary cystadenoma". In the first edition of the Fascicle on Tumors of the Liver and Intrahepatic Bile Ducts, the term biliary cystadenoma was applied to this group. Several histologic categories of cystadenoma are recognized: (1) hepatobiliary cystadenoma with mesenchymal stroma; (2) hepatobiliary cystadenoma without mesenchymal stroma; and (3) an intraductal polypoid hepatobiliary cystadenoma. Hepatobiliary cystadenomas occurring in women usually have mesenchymal stroma, although sufficient sections must be taken to observe the characteristic feature, which is not present throughout the wall. Men with hepatobiliary cystadenoma have the variant lacking mesenchymal stroma and the lining epithelium often has eosinophilic cytoplasm. Intraductal polypoid hepatobiliary cystadenoma has mesenchymal stroma and is recognized in an early stage because of jaundice. This third type may be a variant of the first category because both have mesenchymal stroma and occur exclusively in women. Development of adenocarcinoma occurs with both the first and second category, but seems more common in the latter group.

Definition. Hepatobiliary cystadenoma is a multilocular intrahepatic cyst lined by benign cuboidal or columnar nonciliated epithelium. In men, the underlying fibrous stroma is often hyalinized, whereas hepatobiliary cystadenoma in women usually has densely cellular stroma adjacent to the epithelium (cystadenoma with mesenchymal stroma variant).

Incidence. Hepatobiliary cystadenoma is uncommon, with many case reports and approximately 70 patients recorded by 1984. Several larger series of hepatobiliary cystadenoma have been published including 17 patients by Wheeler and Edmondson (1985) and 14 patients by Ishak and associates.

Clinical. In our series of 17 female patients with hepatobiliary cystadenoma with dense mesenchymal stroma, a wide age range was recorded (19-67 years, with an average of 41.7 years). The duration of symptoms was 2 weeks to 10 years, with abdominal discomfort in 87 percent and pain in 53 percent of the patients. Jaundice occurred in two patients, one associated with a large hilar lesion and the other a result of extrahepatic biliary tract obstruction by the mass. An abdominal mass was palpable in six patients, localized to the left upper quadrant in one patient. Special studies included the angiographic demonstration of an avascular mass, the presence of a mass defect by liver/spleen scan, and the ultrasonic detection of a cystic lesion with dense walls (Forrest et al.). Of our seven patients with hepatobiliary cystadenoma without mesenchymal stroma, the mean age was higher (53.4 years) and there was no female predominance (five males, two females).

Pathogenesis. The origin of hepatobiliary cystadenoma is unknown. If this lesion arises from primitive foregut rests, then other foregut organs would be expected to have histologically similar cysts, as has been observed in the pancreas (Wheeler and Edmondson, 1984). A congenital origin has been proposed by many authors, a concept supported by the concurrence of anomalous bile duct lesions. Alternatively, an acquired origin of the cysts is suggested by the experimental production of similar cysts in rats fed aflatoxin (Cruickshank and Sparshott). The presence of ovarian-like stroma in hepatobiliary cystadenoma has raised the possibility of intrahepatic ectopic ovarian tissue.

Gross. The size of hepatobiliary cystadenomas in our series ranged from 7 to 25 cm in diameter. The left lobe was the site of 65 percent of the lesions and two occupied both lobes. Although 71 percent appeared grossly multilocular, the remainder contained intramural loculi on microscopic examination. The external surface was smooth, with delicate vascularity, and the surface color was reported as white, gray-white, yellow, or yellow-brown. A smooth or trabeculated internal surface was typical, although sessile or polypoid cysts projected into the lumen in occasional cases (pl. II-B; fig. 52). The presence of dense, solid, polypoid masses in the internal wall reflects malignant change, which occurred in two of our 17 patients. Individual loculi ranged from a few millimeters to 18 cm in diameter and usually communicated with each other. The fluid content, ranging from 700 to 4200 ml, was clear or turbid, mucinous, gelatinous, and rarely serous.

Microscopic. Histologic diagnosis is based on the recognition of two distinct layers: epithelial and stromal. The epithelium is cuboidal or columnar, nonciliated, has a small, basally oriented nucleus, and clear mucin-containing cytoplasm (fig. 53). The cystadenoma with mesenchymal stroma variant has a subepithelial stroma that is densely cellular and resembles ovarian stroma composed of closely packed, round- to spindle-shaped cells with little intervening collagen and prominent vascularity. This distinctive stroma

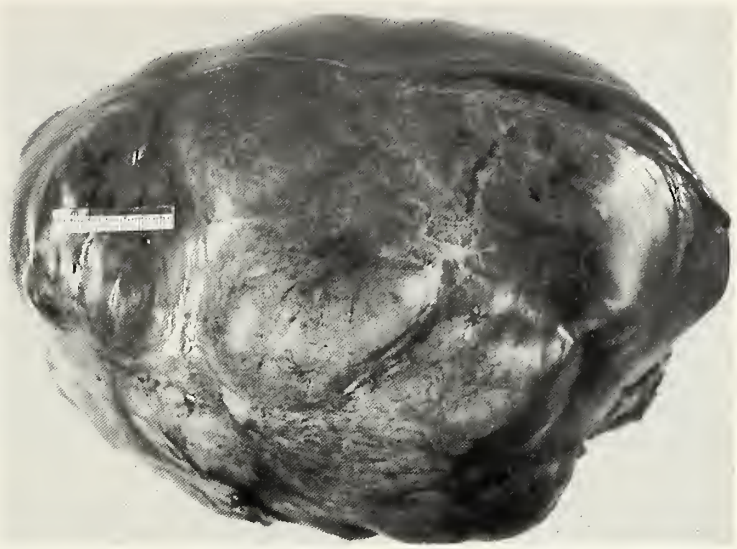


Figure 52
(Figures 52-54 and Plate II-B
are from the same patient)
HEPATOBILIARY CYSTADENOMA

Multilocular mucinous hepatobiliary cystadenoma was diagnosed in a 67 year old woman who had pain and swelling of the right upper abdomen for 2 weeks. A left hepatic lobectomy included a large multilocular cyst which was 21x17.5x10 cm in size and weighed 2670 g. The external surface has multiple bulging nodules. (Courtesy of Dr. Richard Myers, Van Nuys, California.)

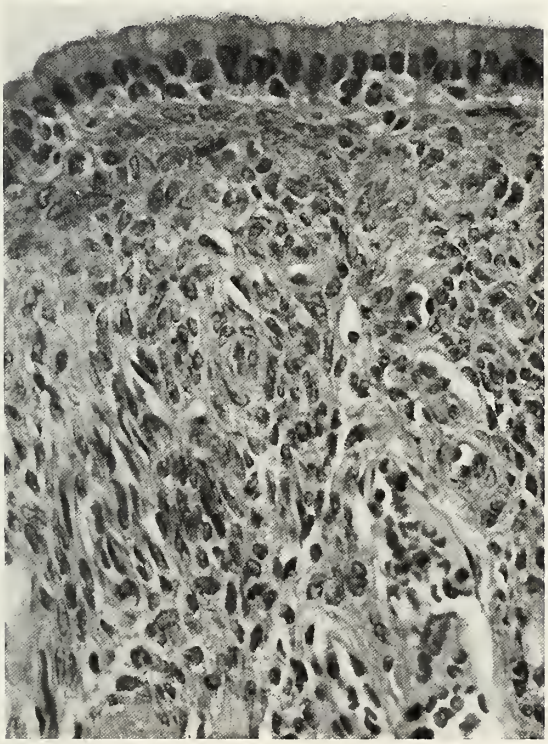


Figure 53
HEPATOBILIARY CYSTADENOMA

High magnification of a hepatobiliary cystadenoma shows bland mesenchymal stroma, spindle cells, and simple cuboidal epithelial lining. X1240. (Courtesy of Dr. Richard Myers, Van Nuys, California.)

varies from 1 to 3 mm in thickness, although it may be completely absent in many areas. Knob-like projections of the primitive mesenchymal stroma may extend into some cyst cavities (fig. 54). A peripheral rim of densely collagenous fibrous tissue is present, which, in addition to deposits of hemosiderin and accumulations of macrophages, may contain small cystic inclusions lined by bland cuboidal epithelium (fig. 55). The presence of pigmented macrophages and cholesterol clefts reflects previous hemorrhage and necrosis. Hyalinization may occur as a thin, subepithelial band, as observed in five of our patients, or as broad septae, frequently calcified. The adjacent liver often contains prominent large vessels and bile ducts in fibrous stroma, which results from pressure atrophy of hepatocellular parenchyma and preservation of the intervening biliary and vascular structures.

Papillary adenocarcinoma occurred in four of our 17 patients. A transition between benign and malignant areas was identified and invasion through the capsule was observed. These patients were generally older, which suggests that malignant transformation requires at least several years. Although pseudostratification and complex papillary growth were present, the malignant cells appeared remarkably bland. Mitoses were inconspicuous. Pseudostratification and elaborate papillary formation were present. (See Cystadenocarcinoma).

Variants. Intraductal cystadenoma, a polypoid intraductal tumor that often occurs with an associated intrahepatic cystadenoma, occurred in four of our patients (Wheeler and Edmondson, 1985). Intraductal cystadenoma may occur with no other lesion, but jaundice is the major clinical symptom. The polypoid tumor fills a major hepatic duct and can be removed. The distinctive gross appearance is that of an intraductal, multicystic polyp. The histologic features are similar to those of hepatobiliary cystadenoma, except for the absence of a fibrous capsule (figs. 56, 57).

Hepatobiliary cystadenomas in men are less common than in women and are often the subject of case reports (Clagett and Hawkins; Corrin; Forrest et al.; Ishak et al.). The reported ages range from 6 to 78 years and long-standing abdominal swelling is the most common clinical manifestation. The tumor may attain a large size; one unreported patient had a tumor 22 cm in diameter and weighing 1700 g. The histologic features differed from the hepatobiliary cystadenoma in women because the mesenchymal stroma was lacking, although the epithelial lining was identical (figs. 58, 59). In three men, the epithelial lining was eosinophilic columnar cells rather than the usual clear cytoplasm of the majority of cysts.

Differential Diagnosis. The major considerations in the histologic differential diagnosis are ciliated foregut cyst, intrahepatic choledochocyst, and parasitic cysts. The hepatic ciliated foregut cyst is distinguished by unilocular growth and a ciliated epithelial lining (Wheeler and Edmondson, 1984). Ciliated foregut cysts are more commonly located in the esophagus or bronchus rather than within the liver. Parasitic cysts are characterized by a fibrous capsule devoid of any epithelial lining and parasitic remnants are within the cavity. Intrahepatic choledochocyst is an intrahepatic extension of a bile duct cyst often located at the hilum and mesenchymal stroma is absent.

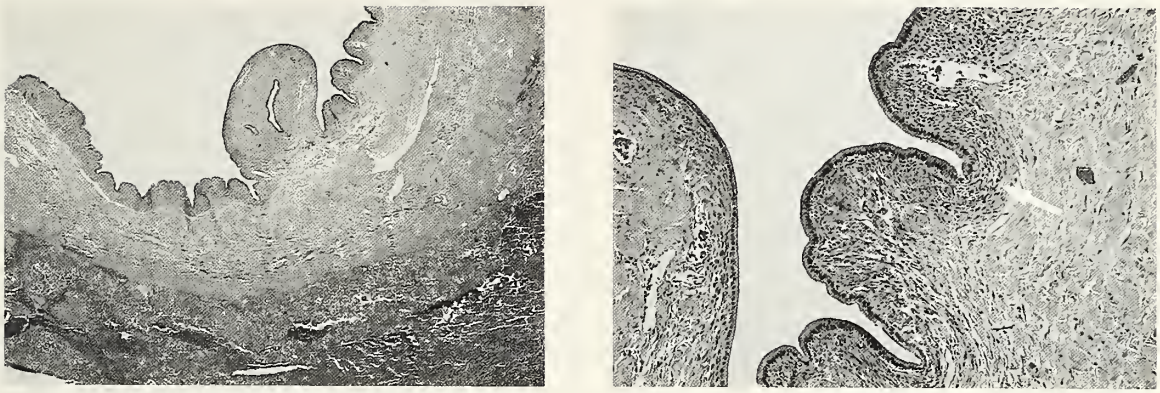


Figure 54
HEPATOBILIARY CYSTADENOMA

A. Lower magnification of a hepatobiliary cystadenoma reveals multiple bulging nodules protruding into the lumen and a thin epithelial lining. X40. B. This hepatobiliary cystadenoma has a mesenchymal stroma beneath the thin epithelial lining and a hyalinized layer below the mesenchymal stroma. X210. (Courtesy of Dr. Richard Meyers, Van Nuys, California.)

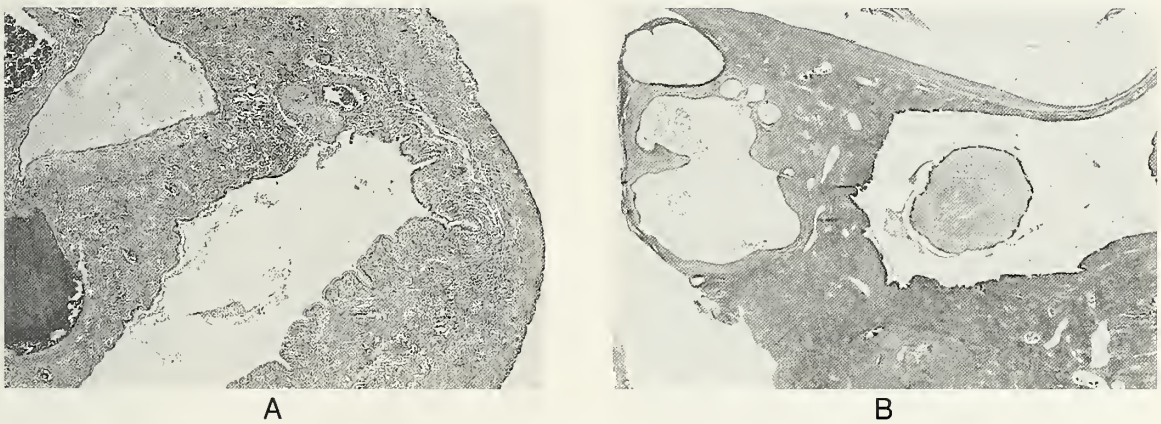


Figure 55
HEPATOBILIARY CYSTADENOMA

A. Multiple cysts with a thin epithelial lining are noted in this hepatobiliary cystadenoma resected from the right lobe of a 60 year old woman. It contained 700 ml of chocolate-colored fluid and the fibrous wall included many small cysts. X85. (Courtesy of Dr. Burton C. Dyson, Wausau, Wisconsin.) B. A large multilocular hepatobiliary cystadenoma, measuring 25 cm in diameter, contained 4200 cc of "muddy" fluid. The wall contained numerous small cysts with flattened cuboidal epithelial lining. X85. (Courtesy of Dr. James Roberts, Torrance, California.)

Figure 56
(Figures 56 and 57 are from the same patient)
HEPATOBILIARY CYSTADENOMA

An intraductal polyp was removed from the left hepatic bile duct with prolapse into the common bile duct producing obstructive jaundice. There is abundant stroma with numerous small cysts lined by cuboidal epithelium. The 37 year old woman had recurrence of a cyst which was entirely removed 4 months later. X85. (Courtesy of Drs. Dubose Dent and Fred Turrill, Glendale, California.)

Figure 57
HEPATOBILIARY CYSTADENOMA

Higher magnification of the hepatobiliary cystadenoma polypoid type noted in figure 56 shows simple columnar epithelium with no atypia and underlying mesenchymal stroma. X420. (Courtesy of Drs. Dubose Dent and Fred Turrill, Glendale, California.)

Figure 58
HEPATOBILIARY CYSTADENOMA

In this large hepatobiliary cystadenoma from a 36 year old man, there are numerous small cysts within the thick fibrous wall. The 22x18x18 cm cyst contained light gray, mucinous fluid. The patient was well 9 years after resection. X85.

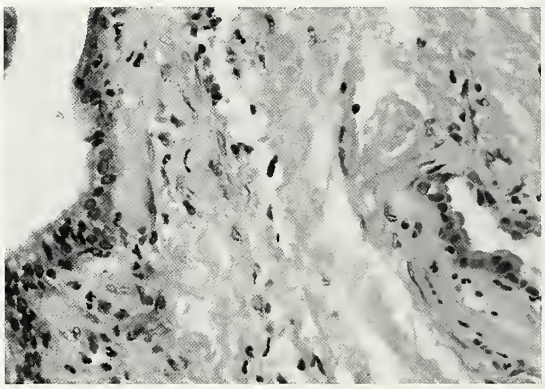


Figure 59
HEPATOBILIARY CYSTADENOMA

This hepatobiliary cystadenoma in a man lacks the mesenchymal stroma typical of the cyst arising in women. The fibrous stroma has little cellularity. Sometimes the columnar or cuboidal epithelium is eosinophilic. X840. (Courtesy of Dr. C.A. Monnin, Jr., Coral Gables, Florida.)

Prognosis. The tumor was excised in 12 of 17 patients in our series. Recurrence was noted in the intraductal variants if only a portion of the intraductal lesion was removed. In such patients, a remnant or an unrecognized multilocular cyst regrew and again produced obstruction. Total excision of the hepatobiliary cystadenoma is advised in order to preclude recurrence or transition to malignancy (Malt).

CONGENITAL HEPATIC FIBROSIS AND POLYCYSTIC LIVER DISEASE

SYNONYMS AND RELATED TERMS: Microcystic liver disease; hepatobiliary fibropolycystic disease.

Congenital hepatic fibrosis is a part of a spectrum of hepatic cystic disease. In polycystic liver disease, in addition to numerous diffuse parenchymal cysts 2 to 4 cm in diameter, the surrounding tissue contains areas of von Meyenberg complexes, which suggests overlap with congenital hepatic fibrosis. Furthermore, there is an overlap in morphologic expression of congenital hepatic fibrosis and diffuse dilatation of major intrahepatic bile ducts (Caroli's disease).

Definition. Congenital hepatic fibrosis is a developmental anomaly of the limiting plate characterized by aberrant bile duct proliferation and periductal fibrosis. The extent of hepatic involvement ranges from a limited sporadic or even sporadic portal area with von Meyenberg complex to diffuse involvement of all lobes of the liver (fig. 60).

Incidence. The incidence is difficult to determine due to varying degrees of expression. Fully developed lesions involving the entire liver are not common and account for less than 1 percent of portal hypertension in most adult series. With increasing use of specialized procedures such as CT scans, more hepatic and renal cystic conditions of asymptomatic patients will be identified, including the spectrum called congenital hepatic fibrosis (Summerfield et al.).

Clinical. The majority of clinically symptomatic patients present in childhood with bleeding esophageal varices or other manifestations of portal hypertension (Kerr et al.). In adults, the lesion is often identified incidentally at autopsy or during surgery

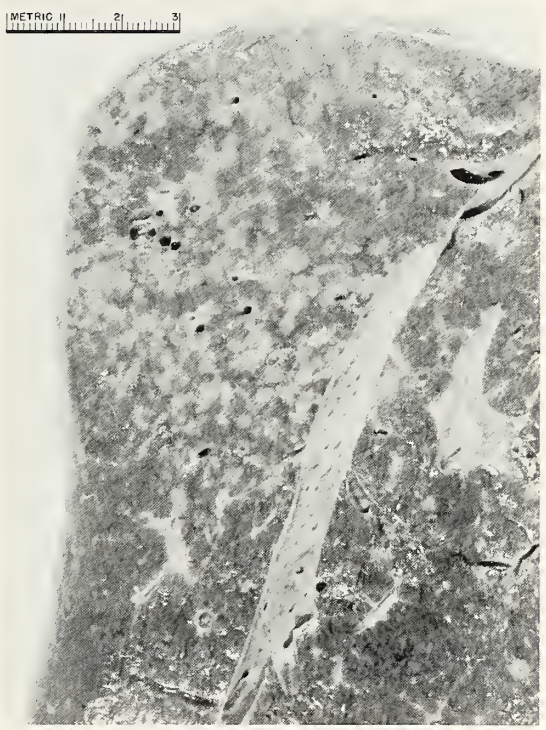


Figure 60
CONGENITAL HEPATIC FIBROSIS
Multiple gray-white, irregular fibrous areas are interconnected and are the portal fibrous tracts containing the microcysts of von Meyenberg complexes. The surface is retracted slightly and the cut surface of liver has a variable degree of fibrosis which is noted in the left upper part of the liver, whereas the lower part appears uninvolved. (Fig. 165 from Fascicle 25, First Series.)

for another condition, although a few have a complication such as cholangiocarcinoma (Daroca et al.). Many (up to 70 percent) of the patients have cystic disease of the kidney as well. In addition, because congenital hepatic fibrosis appears related to Caroli's disease, symptoms related to cholangitis and obstruction may identify additional patients. A rare patient may have marked dilation of an intrahepatic bile duct and further enlargement produces an intrahepatic choledochal cyst.

Pathogenesis. Congenital hepatic fibrosis is often transmitted as an autosomal recessive trait and families account for one-half of all cases. Thus, a developmental anomaly is likely. Chemical compounds have been demonstrated to produce cystic disease in the liver, kidney, and pancreas (McGeoch and Darmady). Jorgensen, in an extensive review, indicated that von Meyenberg complexes may arise from a different pathway than the ductal plate malformation that produces congenital hepatic fibrosis.

Pathology. The external surface of the liver is rippled with slight, fibrous, gray-white depressions. Upon sectioning, a diffuse network of the thin fibrous areas is present throughout the liver (fig. 61). Individual cysts are not visible without a hand lens. Microscopic features are characterized by the presence of the numerous irregular cysts lined by simple cuboidal epithelium, often with prominent intraluminal bile concretions, and surrounded by abundant fibrous tissue lacking portal venous spaces (figs. 62, 63). In the advanced condition, fibrous strands connect the portal tracts. Whereas cirrhotic liver contains true regenerative nodules, terminal hepatic veins are easily identified in congenital hepatic fibrosis.

Variants. The von Meyenberg complex, also called microbiliary hamartoma, is the basic unit of congenital hepatic fibrosis and may occur as either isolated or multiple lesions (figs. 64, 65). Limited development of the condition includes involvement of one lobe and, in these limited forms, clinical symptoms may be less apparent.

Polycystic liver disease is another variant of hepatic cystic disease in which numerous small and large cysts coexist (pl. II-C). The large cysts may be diffuse or involve only one lobe. The fluid content is clear, without bile, and the epithelial lining is cuboidal or flattened cuboidal cells with scant surrounding fibrous tissue (fig. 66). Von Meyenberg complexes are scattered within the fibrous tissue. This condition is often an incidental finding.

Differential Diagnosis. The gross appearance of congenital hepatic fibrosis may be bland and considered normal liver by casual inspection. Microscopic features strongly resemble cirrhosis and the numerous dilated bile ducts often suggest biliary cirrhosis to the unwary. The absence of true regenerative nodules, the absence of portal veins, and the diffuse fibrosis are features that distinguish congenital hepatic fibrosis from cirrhosis. Bile duct adenoma differs because it is usually solitary, and its bile duct structures are smaller, not tortuous, usually have less fibrosis, and grow around and include true portal areas (the remnants can be noted).

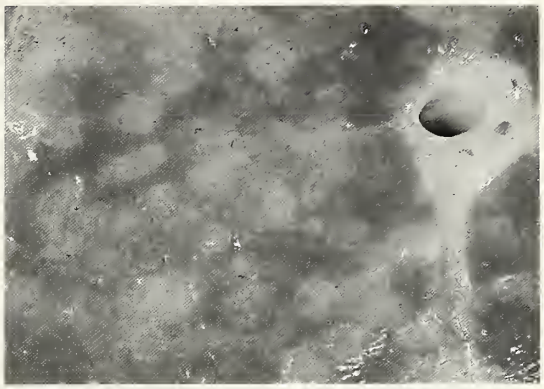


Figure 61
CONGENITAL HEPATIC FIBROSIS
Congenital hepatic fibrosis is seen by the cut surface of a liver with multiple depressed, white, fibrous areas, usually less than 1 mm in diameter, which mimic metastatic carcinoma or Hodgkin's disease. (Courtesy of Dr. David Kaminsky, Rancho Mirage, California.)

Figure 62
(Figures 62 and 63 are from the same patient)
CONGENITAL HEPATIC FIBROSIS
Congenital hepatic fibrosis with marked fibrosis extending between portal areas with von Meyenberg complexes is shown. This 48 year old woman had repeated attacks of cholangitis and the portal areas have an increased inflammatory component. X60. (Courtesy of Dr. James Redwine, Harbor City, California.)

Figure 63
CONGENITAL HEPATIC FIBROSIS
This figure shows congenital hepatic fibrosis with numerous irregular, dilated bile ducts and abundant fibrosis containing moderate numbers of lymphocytes and acute inflammation. X620. (Courtesy of Dr. James Redwine, Harbor City, California.)

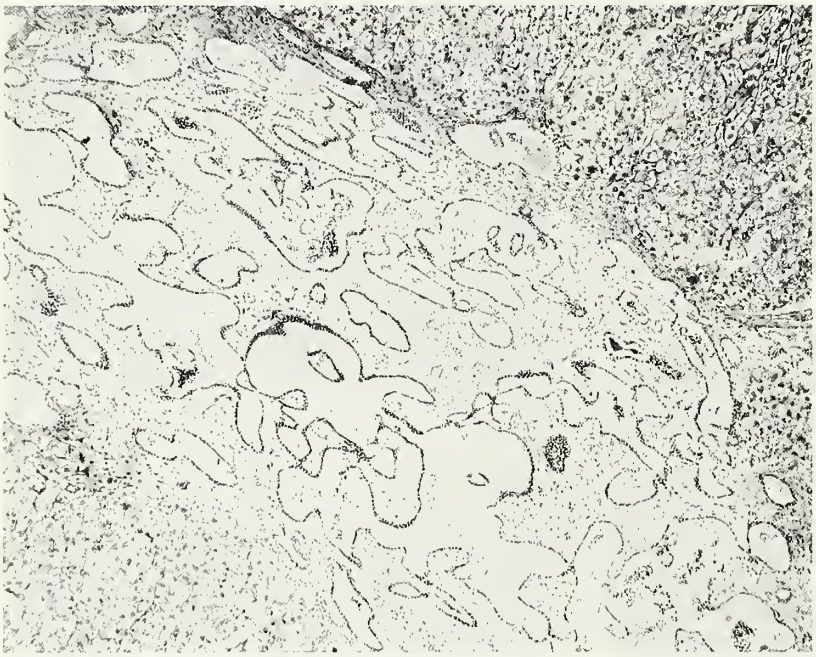


Figure 64
(Figures 64 and 65
are from the same patient)
VON MEYENBERG COMPLEX
This large von Meyenberg complex shows a tortuous pattern of irregular cystic spaces with a thin cuboidal epithelial lining sharply separated from the adjacent liver. X70. (Courtesy of Dr. Karen Cove, Los Angeles, California.)

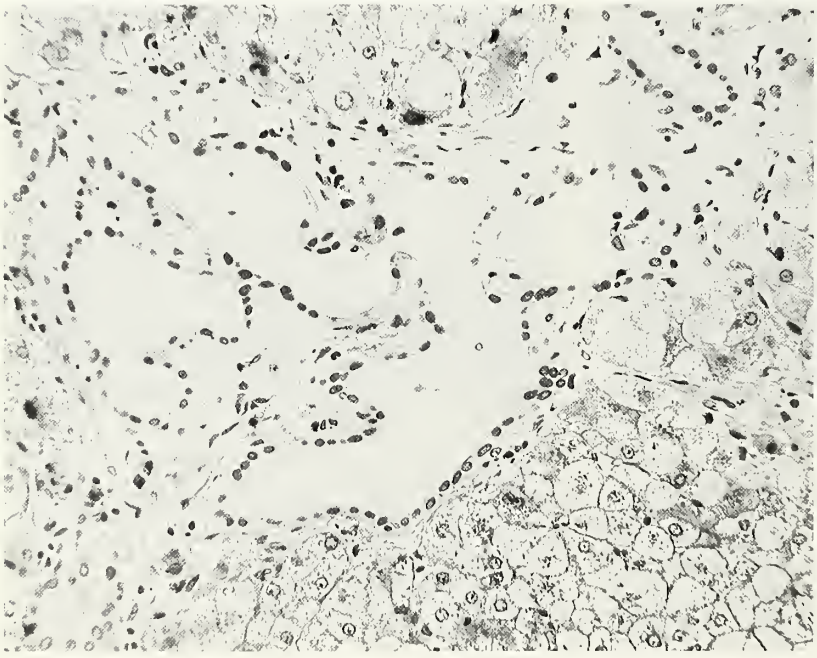
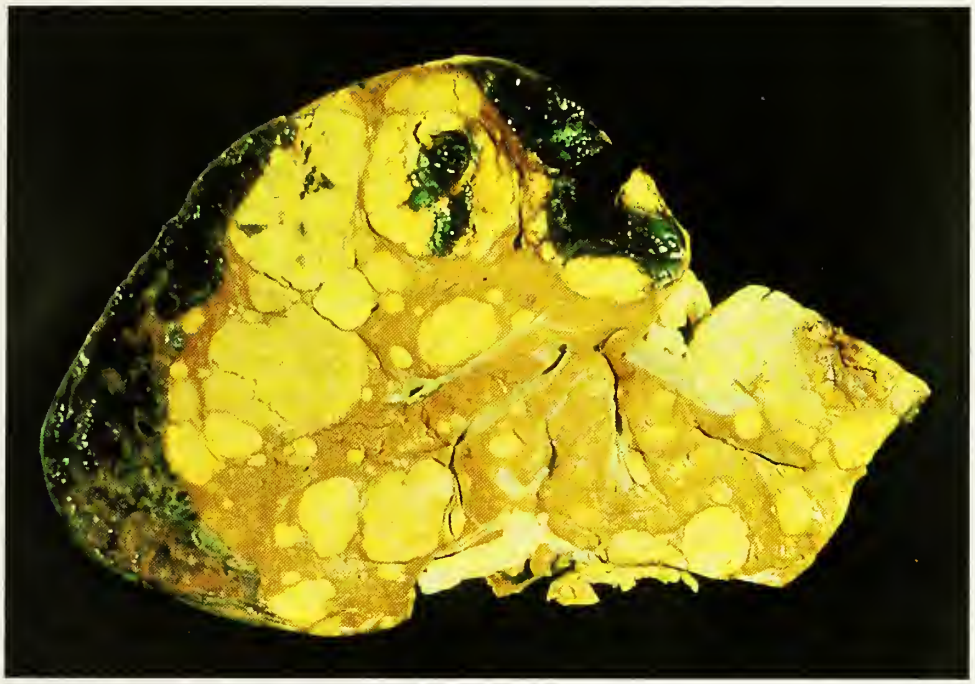


Figure 65
VON MEYENBERG COMPLEX
This von Meyenberg complex has numerous collapsed cystic spaces within fibrous tissue of portal tract lacking portal venous spaces. X200. (Courtesy of Dr. Karen Cove, Los Angeles, California.)

PLATE II



A. MULTIPLE HEPATOCELLULAR ADENOMATOSIS

(Plate II-A and figures 48, 49 are from the same patient)

A cut surface of liver with numerous hepatocellular adenomas, subcapsular hemorrhage, and necrosis from a 39 year old woman with no history of oral contraceptive use. (Courtesy of Dr. Al Lui, Torrance, California.)

B. HEPATOBILIARY CYSTADENOMA

(Plate II-B and figures 52-54 are from the same patient)

The internal surface of this multilocular hepatobiliary cystadenoma is markedly trabeculated. (Courtesy of Dr. Richard Myers, Van Nuys, California.)

C. POLYCYSTIC LIVER DISEASE

(Plate II-C and figure 66 are from the same patient)

The external surface of liver from a 78 year old woman who also had polycystic renal disease shows many simple cysts (1-5 cm) with clear, yellow fluid and a few with dark fluid, apparently due to hemorrhage.

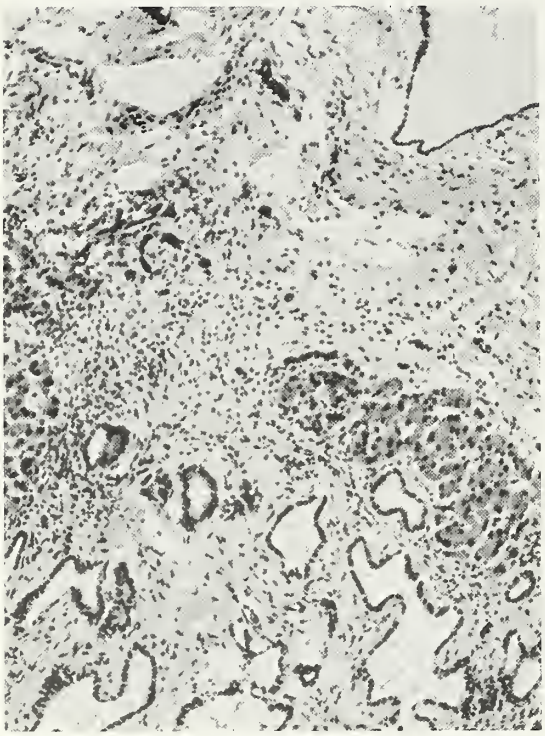


Figure 66
(Figure 66 and Plate II-C are from the same patient)
POLYCYSTIC LIVER DISEASE
Polycystic liver disease has a fibrous wall around the large cysts. The fibrous wall often contains numerous dilated small cysts. X310.

BILE DUCT ADENOMA

SYNONYMS AND RELATED TERMS: Benign cholangioma; tubular adenoma; cholangioadenoma.

Definition. Bile duct adenoma is a benign, usually solitary, subcapsular small nodule, composed of small bile ducts, and discovered incidentally.

Incidence. Bile duct adenoma is a rare tumor recognized in 4 of 50,000 autopsies at LACUSC-MC. Large series have been published: 68 and 52 at the AFIP (Allaire et al.; Ishak and Rabin) and 16 at the USC Liver Unit (Govindarajan and Peters).

Clinical. No symptoms or signs are attributed to the lesion and the tumors were incidental findings either at surgery (29/68) or autopsy (39/68). In the largest published series, men predominated, but in the USC series, the sex distribution was nearly even.

Pathogenesis. The cell of origin is difficult to discern. In some examples, the bile duct adenoma cells appear to show transition forms to hepatocytes. Bile duct cells have more darkly staining nuclei and less abundant cytoplasm. Furthermore, portal bile ducts remain intact and do not demonstrate transition forms to the proliferating bile duct adenoma glandular structures.

Gross. The majority of bile duct adenomas are less than 1 cm in diameter, but lesions as large as 2 cm have been noted. The average size is 5.8 mm and most are subcapsular (Allaire et al.) Multiple lesions occur in a few patients and either lobe of the liver may be involved.

Microscopic. Bile duct adenoma is composed of small ductal structures in the portal area with each duct having a few thin collagen strands at its margin (fig. 67). No capsule is noted, but the nodule is well-demarcated from the adjacent normal liver. Demarcation from the adjacent hepatic cords is sharp with no invasion of the cords by the duct structures. Mitosis is very rare and the nuclei are uniform in size. Lymphocytes and neutrophils may occur in large numbers. Extension of the fibrous stroma and ductular structures to adjacent portal areas reflects spread of the tumor along the portal tracts and not metastasis (fig. 68).

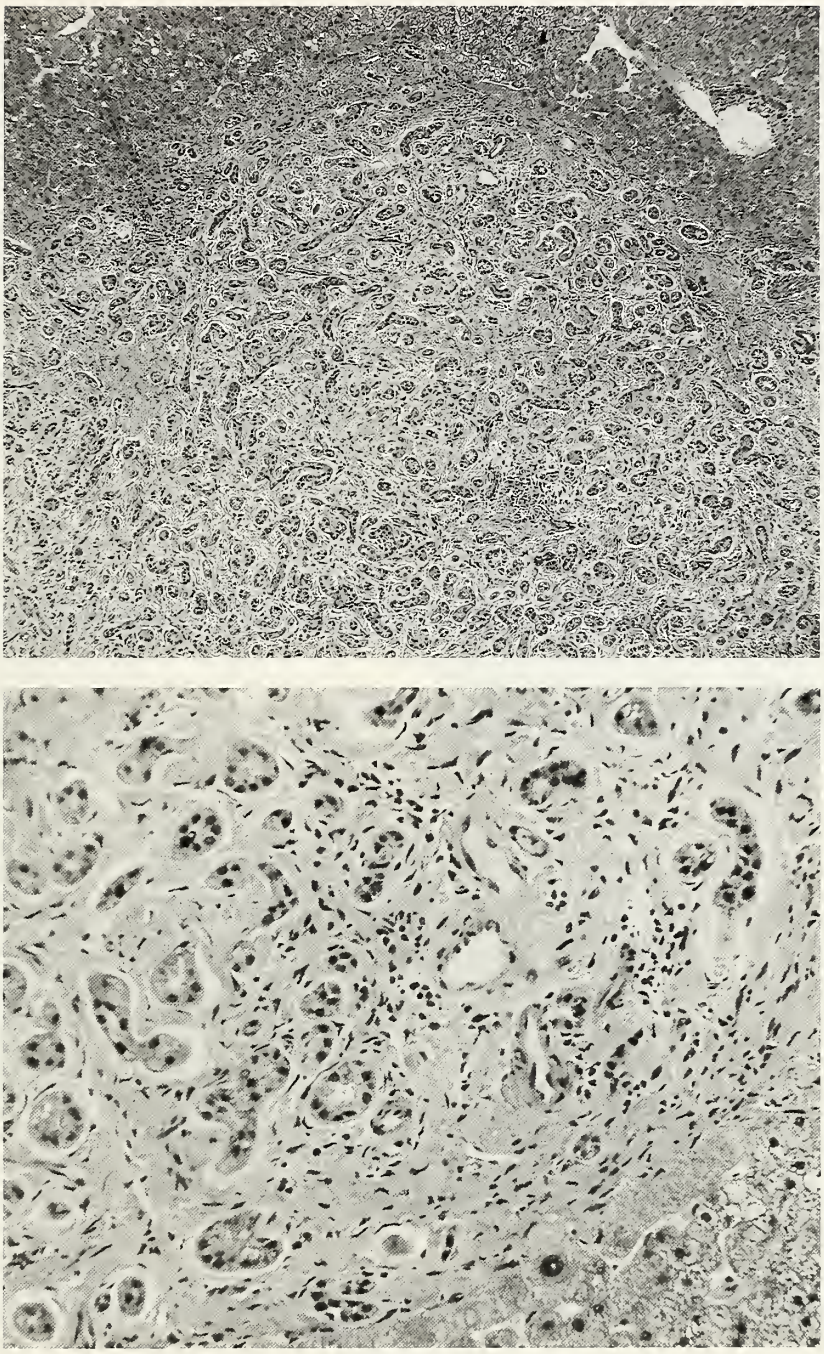


Figure 67
BILE DUCT ADENOMA

A. This bile duct adenoma was a 1 cm in diameter subcapsular nodule. The well-defined lesion was not encapsulated. X70. (Courtesy of Dr. Dick Lee, New Westminster, British Columbia, Canada.) B. The bile duct adenoma is made up of small tubular structures composed of glands with eosinophilic cytoplasm and small lumens. Some form branching glands, but the glands lack the serpiginous microcystic pattern and bile concretions noted in von Meyenberg complexes. X235.

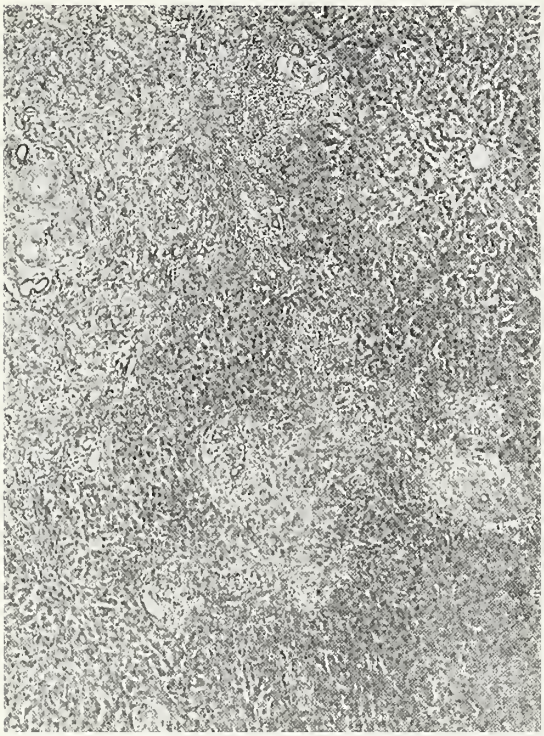


Figure 68
BILE DUCT ADENOMA
A bile duct adenoma with extension of the ductular growth to the adjacent portal area may mimic multiple lesions or suggest invasive growth. This was an incidental finding at cholecystectomy in a 50 year old woman with an isolated nodule that was suspected to be metastatic carcinoma. X60. (Courtesy of Dr. R.J. Taylor, Wichita, Kansas.)

Prognosis. The follow-up on a few patients with removal indicated a benign course. Foucar and associates reported a bizarre case in a 42 year old woman with a large (10 cm) bile duct adenoma. Fifteen years later she was noted to have metastasis and a large cholangiocarcinoma. Transition from benign bile duct adenoma areas to cholangiocarcinoma and undifferentiated carcinoma were identified in this one patient (figs. 69-71).

Differential Diagnosis. The major considerations of such a solitary lesion include von Meyenberg complex, cholangiocarcinoma, and metastatic carcinoma. The von Meyenberg complex is distinguished by serpiginous microcystic ducts and abundant fibrosis. Metastatic carcinoma usually has variation in the amount of fibrosis within the tumor (which is uniform in bile duct adenoma), some dysplastic features, mitosis, and invasion of the adjacent hepatic cords by the glandular epithelium. Cholangiocarcinoma is the most difficult lesion to separate because it may lack dysplastic features and may appear "benign". However, cholangiocarcinoma patients are not recognized until the tumor is more than 2.5 to 5 cm in diameter. At that large size, cholangiocarcinoma usually demonstrates invasive features such as growth within portal vessels and extension of malignant glands into the hepatic cords without a fibrous collar.

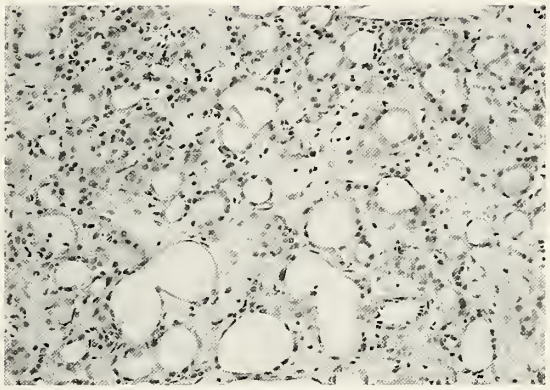


Figure 69
(Figures 69-71 are from the same patient)
BILE DUCT ADENOMA

This bile duct adenoma has abundant fibrous stroma surrounding small glands of simple cuboidal epithelium. This pattern of tumor was documented 14 years prior to the features noted in figures 70 and 71. X420. (Courtesy of Dr. E. Foucar, Minneapolis, Minnesota.)

Figure 70
BILE DUCT ADENOMA

A cholangiocarcinoma in the lower field is separated from an "atypical bile duct adenoma pattern" (that is cholangiocarcinoma) in the upper field by a fibrous band. The glands are so bland that the malignant nature must be discerned from the adjacent fields and presence of metastasis. Above the fibrous bands, the bile duct adenoma pattern merges with overt cholangiocarcinoma (fig. 71). X65. (Courtesy of Dr. E. Foucar, Minneapolis, Minnesota.)

Figure 71
BILE DUCT ADENOMA

The upper portion of the field has small, glandular structures with cuboidal epithelium containing marked basophilic nuclei and cytoplasm, indicative of well-differentiated cholangiocarcinoma. The lower field has solid carcinoma without much fibrous stroma. X420. (Courtesy of Dr. E. Foucar, Minneapolis, Minnesota.)

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BENIGN MESENCHYMAL TUMORS AND TUMOR-LIKE CONDITIONS

Many mesenchymal tumors in the liver (i.e., lipoma, leiomyoma) are classified by the same criteria used for similar tumors occurring outside of the liver. Although benign hepatic vascular tumors are the most common primary hepatic tumor, the incidence of mesenchymal tumors is very low. While many mesenchymal tumors resemble their counterparts in soft tissue, mesenchymal hamartoma is a distinctive hepatic mesenchymal tumor that appears to be a malformation of primitive hepatic mesenchyme.

MESENCHYMAL HAMARTOMA

SYNONYMS AND RELATED TERMS: Bile duct fibroadenoma; lymphangioma; cavernous lymphangiomatoid tumor; giant lymphangioma; cystic mesenchymal hamartoma.

Definition. Mesenchymal hamartoma is a large solitary tumor that occurs in children. It is composed of gelatinous mesenchyme with cyst formation and remnants of hepatic parenchyma.

Incidence. Mesenchymal hamartoma is not common and accounted for 8 percent of childhood tumors in a large multiseries summary of childhood tumors (Dehner, 1978). At The Children's Hospital in Boston, nine examples occurred (5 percent of all childhood liver tumors over a 57-year period) (Lack).

Clinical. A male predominance is noted; Stocker and Ishak reported 69 percent males in a combined published series of 72 patients. The age range, restricted to children, is reported from newborn to 10 years, with an average age of 15 months (Stocker and Ishak). Progressive, painless, abdominal enlargement occurs and radiographic studies confirm a large hepatic mass with multilocular cysts (Ros et al.). One unusual case demonstrated heart failure attributed to arteriovenous shunts within the tumor (Smith et al.). Common blood tests are of no diagnostic help, but ultrasound and CT scans reveal a typical pattern. Angiography demonstrates an avascular center and a hypervascular periphery (Stanley et al., 1986).

Pathogenesis. The term mesenchymal hamartoma has been widely accepted following its introduction in 1956 by Edmondson, who applied it to four cases reported in the first edition of the Fascicle. The predominantly young age indicates a likely congenital defect in hepatic mesenchymal maturation. The stimulus for the mesenchymal proliferation after birth is unknown and may be short-lived. Partial excision of lesions has not always resulted in further enlargement and no example of malignant change has been noted (Stocker and Ishak). Enlargement of the lesions may be attributed to accumulation of fluid within the mesenchymal tissue. The edematous matrix and cystic change has led many to believe that this is a lymphangioma. However, the mixture of elements (bile duct, vessels, and mesenchyma) suggests a more complex origin, and ultrastructural examination provides no support for origin from blood vessels or lymphatic vessels (Dehner et al.).

Gross. The patient usually presents with a large lesion of from 3 to 21 cm in diameter, with an average of 18 cm (Lack). The weight range is 238 to 6810 g, with the average of 19 cases at 1311 g (Stocker and Ishak). The right lobe is more commonly involved (75 percent) and the lesion may be pedunculated (17-30 percent). Multicolored cysts, including gray, blue, and red, bulge from the external surface of the large oval solitary lesions. Although the junction with the normal liver is usually readily apparent, a distinct capsule is not. The cut surface oozes myxedematous fluid and reveals cystic change, except in very young patients, which suggests that the fluid accumulation may be a secondary phenomenon. Round and multiloculated cysts range from a few millimeters to up to 14 cm in diameter, with a lining that varies from smooth and lacy to ragged. The remaining soft tissue is dense yellow-tan to brown. The fluid content is light-yellow to amber (pl. III-A). Hemorrhagic and necrotic tissue is not noted (Stocker and Ishak). Solid areas of the tumors are a mixture of loose, yellow, myxoid tissue with fibrous, white bands and red-tan nodules. Occasionally, at the margin of the mass, there are satellite nodules.

Microscopic. A mixture of cysts, bile ducts, hepatocytes, and edematous mesenchymal tissue with vascular proliferation is noted in the multiple sections of tumor (figs. 72-74). The mesenchymal tissue is comprised of scattered, stellate cells in an edematous matrix containing collagen fibers. Dense areas of mesenchyme contain abundant small vessels and bile ducts. Fat stains are negative in the mesenchymal areas. The cysts appear to be dilated bile ducts or fluid accumulation within mesenchyme without lining and no bile pigment deposition is noted. Satellite lesions adjacent to the main mass may be the result of the mesenchymal proliferation in the portal regions; the center is often an intact bile duct (fig. 74). Hepatocytes appear to be a passive component, irregularly integrated into the mesenchymal component. Plates of hepatocytes are thicker at the margins than in the center where individual cells occur. Bile ducts are prominent at the periphery as well and are frequently single ducts or small cysts with intricate and delicate branching. A transition of bile duct epithelium to hepatocytes is often apparent.

Differential Diagnosis. The prominent vascular component may suggest hemangioendothelioma if a limited sample is available for study. However, the large size of mesenchymal hamartoma contrasts with the infantile hemangioendothelioma, which is smaller and often multiple. The lack of other clinical features (cutaneous hemangiomas, heart failure) and the cystic nature noted by external examination indicate mesenchymal hamartoma rather than hemangioendothelioma. Lymphangioma of liver occurs as an isolated hepatic lesion, usually in adults, and is characterized by diffuse sinusoidal involvement with hepatocellular atrophy and no cystic change.

HEMANGIOMA

SYNONYMS AND RELATED TERMS: Cavernous hemangioma; angioma.

Definition. Cavernous hemangioma is usually a solitary, circumscribed, blood-filled tumor that is lined by endothelium on thin, fibrous stroma and composed of cavernous spaces. It may also have a

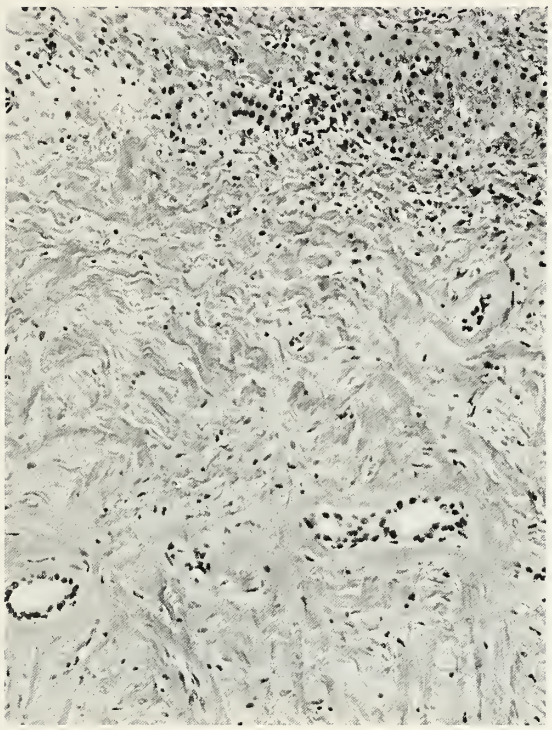


Figure 72
MESENCHYMAL HAMARTOMA
A small group of liver cells, mature connective tissue, and remnants of bile ducts are within the fibrous tissue of this mesenchymal hamartoma. X120. (Fig. 201 from Fascicle 25, First Series.)

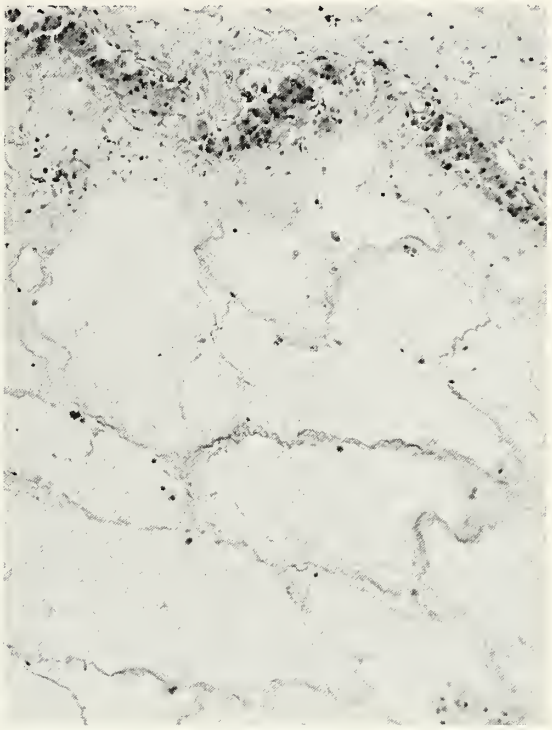


Figure 73
MESENCHYMAL HAMARTOMA
Cyst-like spaces divided by thin, fibrous septa and a finely granular protein precipitate indicate the fluid content in this mesenchymal hamartoma. X120. (Fig. 200 from Fascicle 25, First Series.)

capillary network. Occasionally, diffuse hepatic involvement occurs.

Incidence. Review of the 91,000 autopsies at the LACUSC-MC indicates 850 hepatic cavernous hemangiomas (approximately 1 percent of all autopsies). The reported incidence varies from 0.4 to 20 percent, with the highest incidence reported from a prospective thorough search of livers in 95 consecutive medicolegal necropsies involving men aged 35 to 69 years in Helsinki (Karhunen, 1986).

Clinical. In the large LACUSC-MC autopsy series, there were 525 males and 325 females; patients under 40 years of age were predominantly female. The vast majority of cavernous hemangiomas remain clinically silent because they are small and do not rupture or enlarge. Less than 15 percent of patients are symptomatic, due to a mass lesion or compression of adjacent structures. Many of these patients are discovered to have giant hemangiomas (i.e., more than 10 cm in diameter) and are recognized by specialized radiographic tests (Takayasu et al.). Ultrasound examination may reveal patterns of involution and hyalinization, but sometimes they may mimic small hepatocellular carcinomas. A few patients have

Figure 74
MESENCHYMAL HAMARTOMA
A mesenchymal hamartoma at the margin of the tumor with extension of edematous connective tissue into adjacent portal areas caused distortion of the bile ducts and periportal hepatocytes. A 942 g "cystic" tumor was removed from the right lobe of an 11 month old male infant. X105. (Courtesy of Dr. Randell Davis, Spokane, Washington.)

rupture of the hemangioma (Sewell and Weiss) and needle biopsy is associated with increased bleeding risk. The condition has been discovered incidentally without significant bleeding following needle biopsy (Brambs et al.). Recent thrombosis of some larger hemangiomas is associated with severe thrombocytopenia (fig. 75). In a review of 28 patients with large cavernous hemangiomas, 16 had resection (age range 29-80 years, average 53 years) and 75 percent were women, similar in age and sex distribution to the nonoperated group of 12 (Schwartz and Husser). The majority of cavernous hemangiomas in adults are stable and do not appear to change in size. No enhancement with contrast may be noted in some lesions by CT examination, perhaps due to slow blood flow, central fibrosis, thrombosis, and necrosis (Takayasu et al.).

Pathogenesis. The higher incidence of these tumors in older persons suggests development during later life. The absence of other liver disease indicates they apparently are not the result of chronic necrotizing disease (cirrhosis). However, children are known to develop or have the lesion at

Figure 75
HEMANGIOMA
A thrombus fills the center of a cavernous hemangioma in a 23 year old woman with a platelet count of 75,000/mm^3 and a massively enlarged liver due to two hemangiomas. X75. (Courtesy of Dr. Richard Armstrong, Tucson, Arizona.)

birth (Dehner and Ishak). The natural history of these lesions is variable. Some cavernous hemangiomas seem responsive to hormones and grow during pregnancy; others have been treated with corticosteroids to promote involution. Spontaneous involution occurs in some, especially in the newborn. An ultrastructural study of seven patients revealed the presence of a basement membrane beneath the endothelial cells, which led Kojimahara to conclude that the lesion was a hamartoma.

Gross. Cavernous hemangiomas range in size from a few mm to up to 20+ cm; giant hemangiomas are defined as 10 cm or larger (figs. 76, 77). Ninety percent are solitary and most are visible from the external surface. A few are pedunculated and may present as a puzzling tumor because origin from the liver is not obvious. Cavernous hemangioma is bright red and may collapse when cut. Many large cavernous hemangiomas have a honey-combed cut surface, while others have calcification and dense fibrosis (Plachta). Involution of large cavernous hemangiomas results in dense fibrosis, beginning centrally and spreading until occlusion of the vascular spaces is complete (pl. III-B). During involution, necrosis may occur and the lesion may mimic metastatic tumor (Berry).

Figure 76
HEMANGIOMA
This giant cavernous hemangioma of the right lobe of a 51 year old woman produced a total hepatic weight of 13 kg. Progressive enlargement of the liver occurred over 8 years and the liver extended to the pelvic brim.

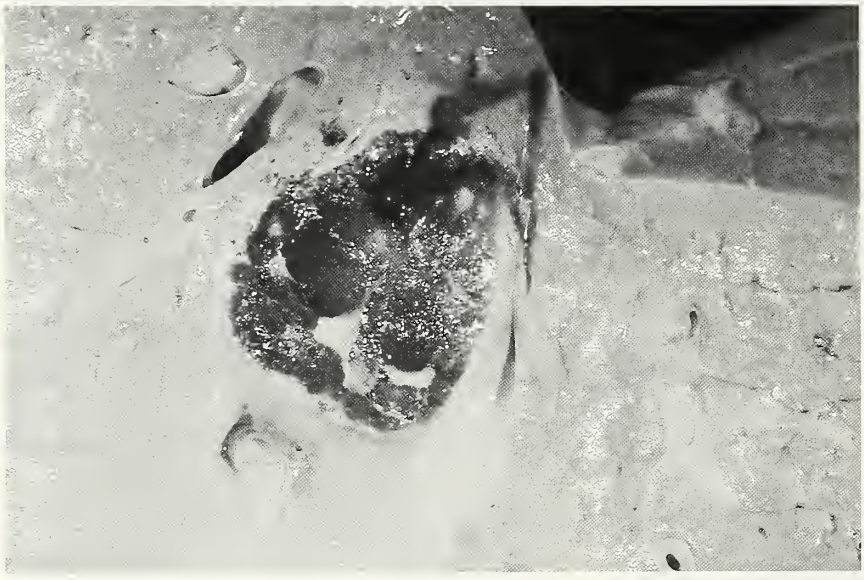
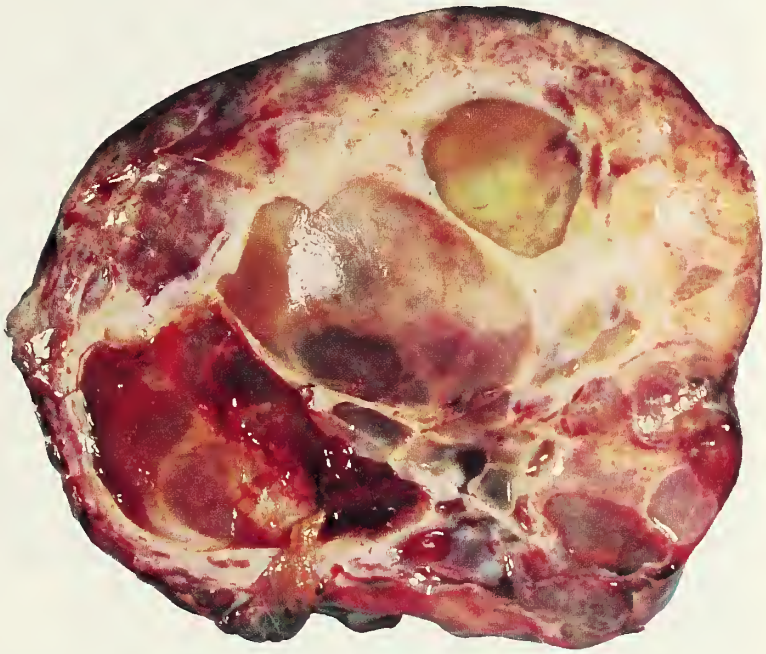


Figure 77
HEMANGIOMA
This cavernous hemangioma with irregular margins is from a 40 year old woman who died of a cerebral hemorrhage.

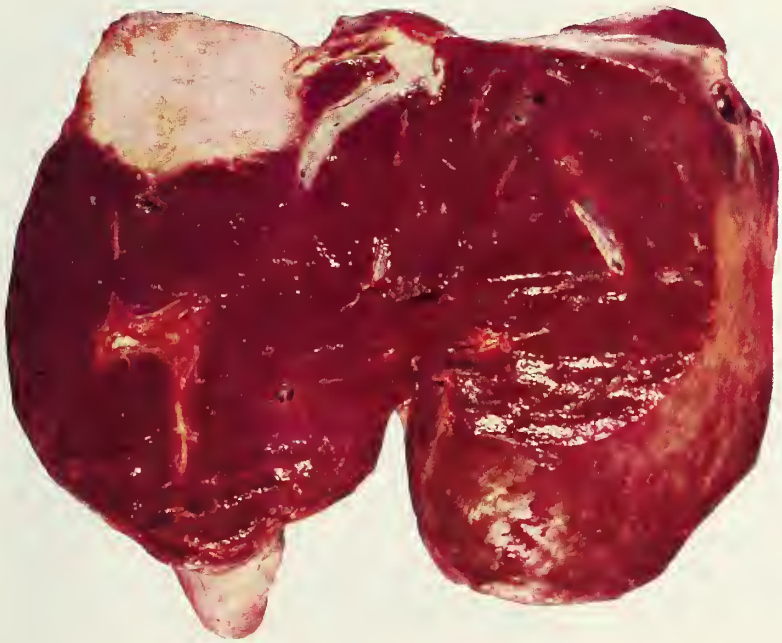
Microscopic. Cavernous hemangiomas are composed of blood-filled spaces of variable size and shape and are lined by a single layer of flat endothelium without atypia or increased cellularity (figs. 78, 79). The septa separating the loculi are often incomplete and are usually thin, poorly cellular, and have a myxoid appearance (fig. 79). The incomplete septa may project into the cavernous spaces like fingers. Major blood vessels (arterial branches) and small bile ducts may occur in larger septa. Some large portal tract branches have arterial branches that merge with the vascular channels, producing arteriovenous shunting (fig. 80). The loculi may contain recent or old thrombi which undergo fibrosis (fig. 81), calcification or ossification. Although most cavernous hemangiomas are well-circumscribed, some have vascular components that extend irregularly into the adjacent parenchyma.

PLATE III



A. MESENCHYMAL HAMARTOMA

A cyst-like space is filled with pale yellow fluid in this mesenchymal hamartoma removed surgically from a 12 month old male. (Pl. V-A from Fascicle 25, First Series.)



B. HEMANGIOMA

Complete replacement by fibrosis of a large hemangioma is shown in a 62 year old woman. The left lobe contains other cavernous hemangiomas without fibrosis. (Pl. V-B from Fascicle 25, First Series.)

Figure 78
(Figures 78 and 79 are from the same patient)
HEMANGIOMA

Cavernous spaces in the hemangioma vary in size and incomplete septa are present in this incidental lesion that was identified in a 62 year old man during gallbladder surgery. X75.

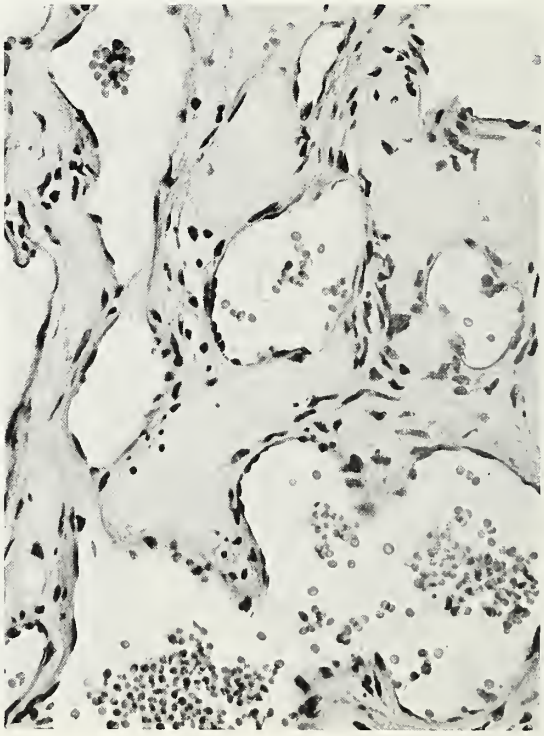


Figure 79
HEMANGIOMA

A higher magnification of figure 78 shows flat endothelial cells lining the vascular channels. The septa are poorly cellular, with myxomatous stroma. X280. (Fig. 106 from Fascicle 25, First Series.)

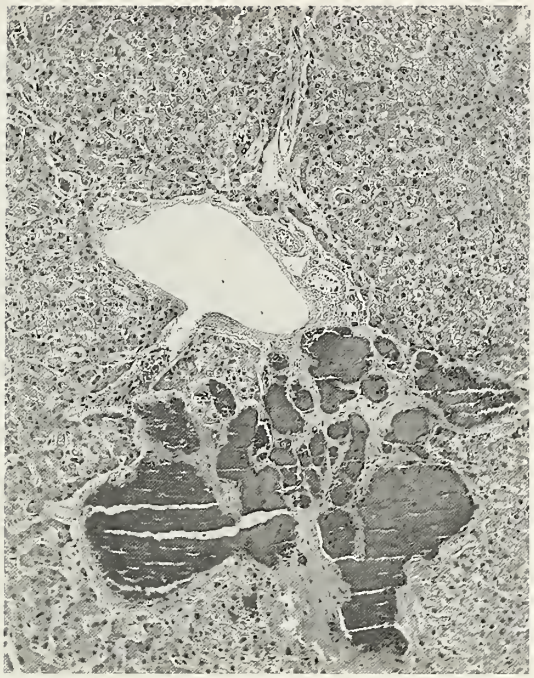


Figure 80
HEMANGIOMA
A small cavernous hemangioma in the periportal area has a portal vein opening into the hemangioma. X52. (Courtesy of Dr. William H. Kern, Los Angeles, California.)

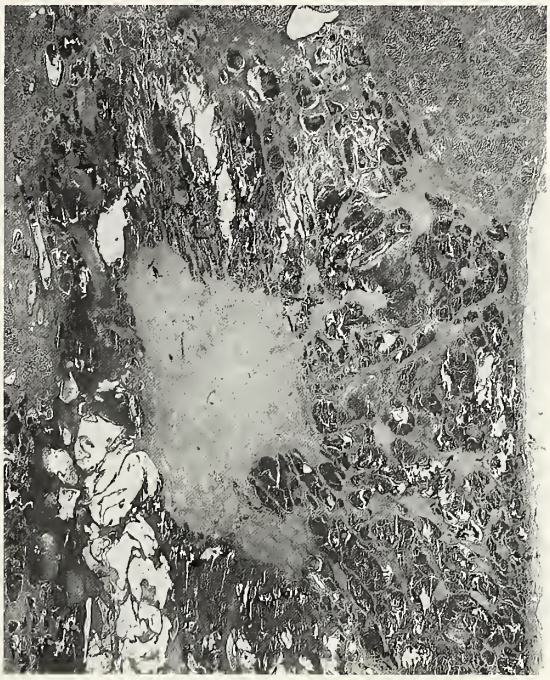


Figure 81
HEMANGIOMA
This early obliterative central fibrosis of a subcapsular cavernous hemangioma was an incidental finding at autopsy. X5.8.

Variants. Sclerosed cavernous hemangioma is rare. In one thorough examination of 1000 consecutive autopsied patients, two fibrous nodules (1 cm and approximately 2.5 cm in diameter) were discovered (Berry). Multiple sections and special stains, such as a reticulin stain, were necessary to identify vascular outlines within the fibrous stroma and to identify the vascular origin (figs. 82, 83).

Diffuse systemic hemangiomatosis is a rare systemic disease of adults, with multiple small hemangiomas occurring in multiple organs including bone, lung, and liver (Kane and Newman; Sugimura et al.). In the case reported by Kane and Newman, the septa between the vascular spaces were thicker and more cellular than usually noted in cavernous hemangioma (fig. 84).

Mixed cavernous and capillary hemangioma of the newborn is rare, with one patient in the LACUSC-MC autopsy series and an additional patient in our consultation files. Great enlargement of the liver was noted at birth. One infant died on the eighth day; the other at 1 month. There is massive replacement of the liver by both cavernous and capillary hemangiomatous growth (pl. IV-A; figs. 85, 86). Large cavernous areas are divided by fields of hepatic cords, with atrophic hepatocytes divided by widened sinusoids containing hematopoiesis. Some hepatocytes had marked cholestasis (fig. 87).

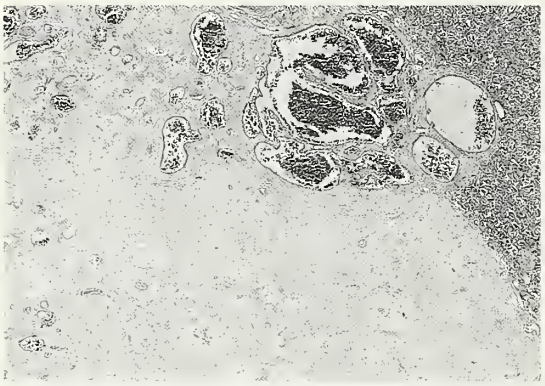


Figure 82
(Figures 82 and 83 are from the same patient)
SCLEROSED CAVERNOUS HEMANGIOMA

This sclerosed cavernous hemangioma, resected in an 88 year old woman, was an incidental finding at surgery. The 4x4x2 cm lesion was located at the inferior margin of the right lobe. Note the abundant fibrosis and a few dilated cavernous spaces near the margin with normal liver. X85. (Courtesy of Dr. M. Montllor, Pasadena, California.)

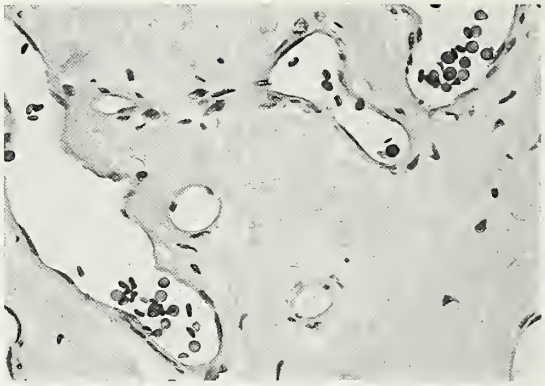


Figure 83
SCLEROSED CAVERNOUS HEMANGIOMA

This higher magnification of the cavernous hemangioma from figure 82 shows sclerosis and scattered, small, vascular channels. No thrombosis was noted in multiple sections. X840. (Courtesy of Dr. M. Montllor, Pasadena, California.)

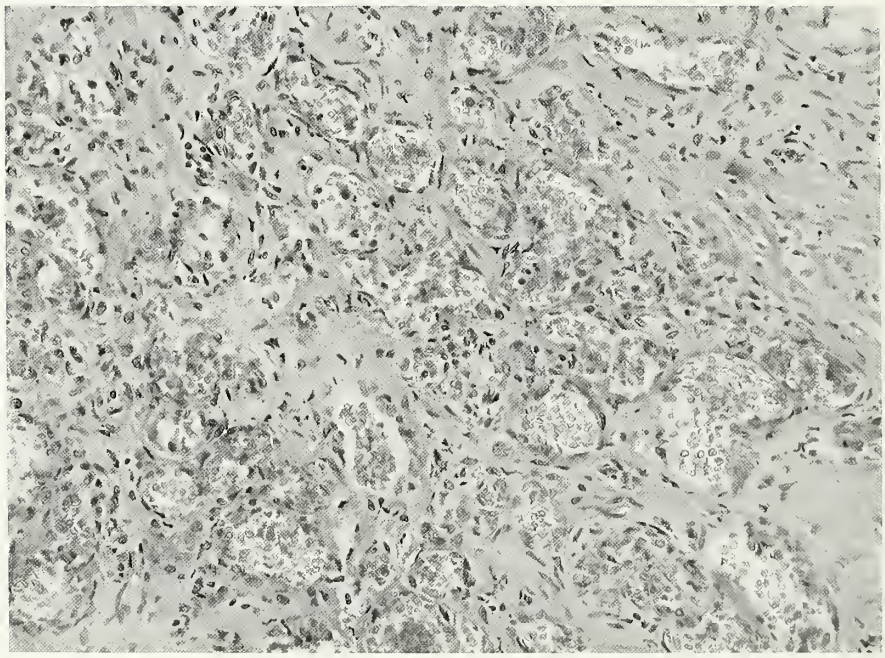


Figure 84
DIFFUSE SYSTEMIC HEMANGIOMATOSIS

The septa between the cavernous spaces are thicker and more cellular than usual and many capillary spaces are formed in this 64 year old woman with diffuse angiomatosis of the liver and skeleton. X250. (Courtesy of Drs. Edward Smuckler and Alan Newman, San Francisco, California.)

Figure 85
(Figures 85 and 86 are from the same patient)
MIXED CAVERNOUS AND CAPILLARY HEMANGIOMA OF THE NEWBORN

Large cavernous hemangiomas interconnect and leave islands of fibrous stroma with other areas of small vascular channels, as seen in figure 86. X85. (Courtesy of Dr. P. Chandrasoma, Los Angeles, California.)

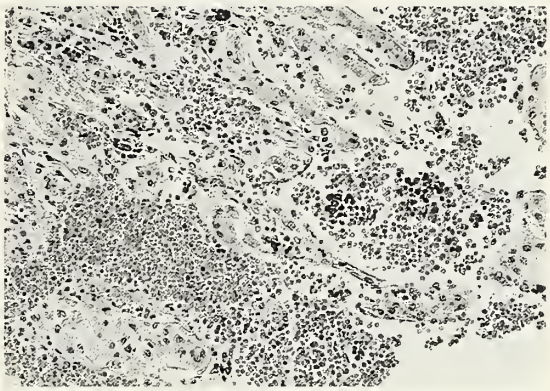


Figure 86
MIXED CAVERNOUS AND CAPILLARY HEMANGIOMA OF THE NEWBORN

Marked sinusoidal stasis with extramedullary hematopoiesis occurs, as well as marked hepatocellular atrophy, in this massive cavernous hemangioma of the newborn. X420. (Courtesy of Dr. P. Chandrasoma, Los Angeles, California.)

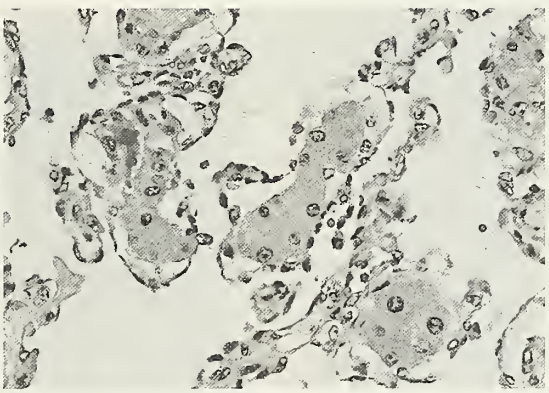


Figure 87
(Figure 87 and Plate IV-A are from the same patient)
MIXED CAVERNOUS AND CAPILLARY HEMANGIOMA OF THE NEWBORN

Marked cholestasis occurs in thin cords of atrophic hepatocytes surrounded by the marked vascular proliferation in cavernous hemangioma of the newborn. X840. (Courtesy of Dr. Al Hirst, Loma Linda, California.)

Differential Diagnosis. Microscopic examination of a hemorrhagic vascular lesion may suggest metastatic Kaposi's sarcoma and angiosarcoma, as well as cavernous hemangioma, peliosis hepatis, and, possibly, hereditary hemorrhagic telangiectasia. Separation of hemangioma into either cavernous or capillary types can be difficult, but the presence of a few cavernous spaces indicates cavernous type. The presence of atypical lining cells with large angulated nuclei indicates angiosarcoma. Kaposi's sarcoma may appear very bland, involves portal areas, and is composed of spindle cells and few vascular spaces. Infantile hemangioendotheliomas are usually not as hemorrhagic as cavernous hemangiomas and have more solid fibrous nodules.

Hereditary hemorrhagic telangiectasia, also called Osler-Weber-Rendu disease, is an inherited condition with multiple organ involvement by hemangiomatous lesions that also affect the liver. Hepatic involvement is rare and, if present, is diffuse with increased portal vascular channels; there are no isolated focal vascular lesions as in cavernous hemangioma. The dilated vascular channels lack the supporting stroma found in cavernous hemangioma; although, sometimes Osler-Weber-Rendu disease has cavernous hemangioma (fig. 88).

Peliosis hepatis, also called angiomatosis hepatis, is the presence of multiple, small (less than 5-10 mm in diameter), dilated, blood-filled cavities that are not necessarily lined by endothelium. There is no supporting stroma as is noted in a hemangioma (fig. 89). Peliosis hepatis occurs at all ages and there is usually no clinical significance. It is associated with a wide variety of conditions, including AIDS

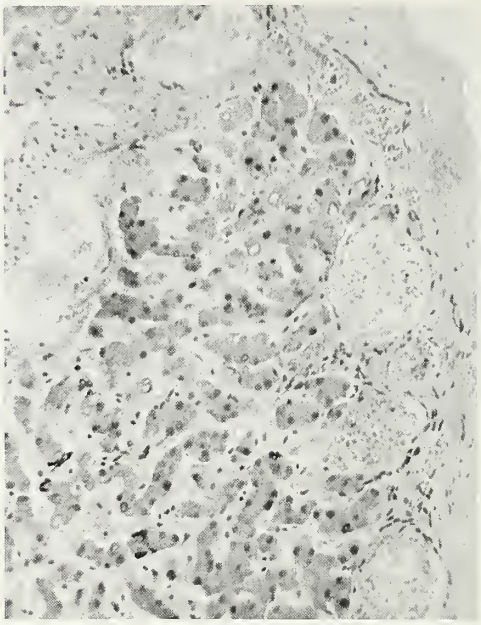


Figure 88
TELANGIECTASIA
Subcapsular telangiectasia in Osler-Weber-Rendu disease with multiple dilated vascular spaces is similar to hemangioma, but lacks septae. X150. (Fig. 102 from Fascicle 25, First Series.)

Figure 89
PELIOSIS HEPATIS
Peliosis hepatis with multiple, dilated, blood-filled sinusoids in a 20 year old man with Fanconi's anemia and 8 months of oxymetholone treatment. He died of hepatic hemorrhage and the liver contained peliosis hepatis characterized by many pale, greenish-yellow, gelatinous nodules, some with blood. X40. (Courtesy of Robert Hunter, Chicago, Illinois.)

(Czapar et al.), anabolic steroid use (Nadell and Kosek), thorotrast use (Okuda et al.), renal transplantation (Degott et al.), and other disorders. The number of lesions varies and marked liver enlargement to 6300 g has occurred (Czapar et al.).

Treatment. Surgical resection, if possible, is advocated for large cavernous hemangiomas greater than 10 cm in diameter (Adam et al.; Malt; Starzl et al.). Rarely, a large cavernous hemangioma produces platelet trapping that requires treatment. The majority of lesions appear very stable and may involute spontaneously (Schwartz and Husser). The use of CT scans and other technics facilitates the diagnosis of many more cavernous hemangiomas than previously noted. Rupture of hepatic hemangioma is rare and leads to surgery for only a few large lesions (Sewell and Weiss). Radiation therapy and hepatic artery ligation are not effective treatments (Schwartz and Husser).

INFANTILE HEMANGIOENDOTHELIOMA

SYNONYMS AND RELATED TERMS: Angioendothelioma; cavernous angioma.

Definition. Infantile hemangioendothelioma is a vascular tumor derived from endothelial cells that proliferate and form many small vascular channels. Ninety percent of infantile hemangioendotheliomas are discovered within the first 6 months of life and affect both males and females. The most common type is multinodular and often involves other organs such as skin, lung, lymph nodes, and bone. Congestive heart failure occurs because of the marked arterial venous shunt, and a very rare complication is associated malignant change. Solitary infantile hemangioendothelioma is an uncommon variant limited to hepatic involvement.

Incidence. Infantile hemangioendothelioma is relatively common and accounts for approximately 12 percent of all childhood hepatic tumors (Dehner, 1978).

Clinical. Females are affected more often than males and half of the patients have hepatomegaly. Other clinical findings include congestive heart failure (up to 25 percent), severe thrombocytopenia (due to trapping of platelets), and rupture with hemoperitoneum (Dachman et al.; Dehner, 1978). Cutaneous hemangiomas occur in 20 to 40 percent of patients (figs. 90, 91) and jaundice (not physiologic) has been reported. Radiographic studies reveal evidence of heart failure and hepatomegaly; some patients have fine, speckled calcification in the liver. Ultrasonography and CT scans have been useful in identifying and following the

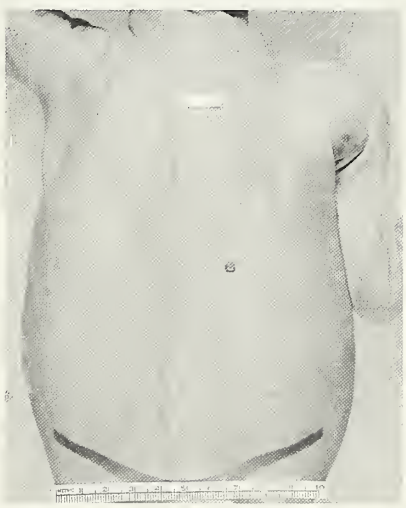


Figure 90
(Figures 90-92 are from the same patient)
INFANTILE HEMANGIOENDOTHELIOMA
This cutaneous hemangioma in a 3 month old girl is bright red. She died of congestive heart failure and had multiple hepatic hemangioendothelioma.

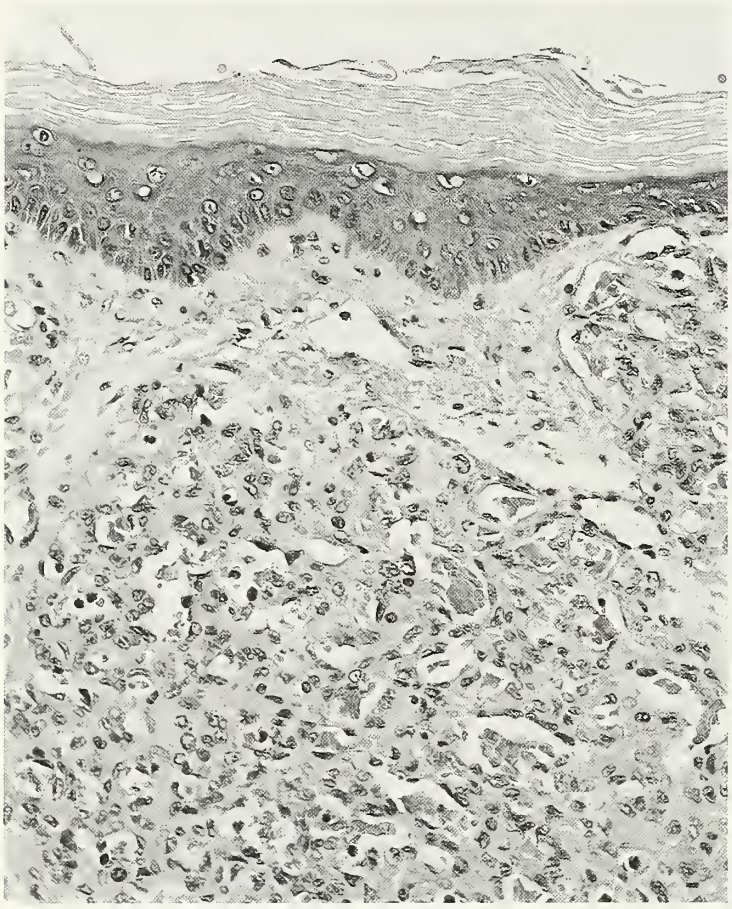


Figure 91
INFANTILE HEMANGIOENDOTHELIOMA
The dermis contains the cutaneous hemangioendothelioma in the same infant noted in figure 90. X260.

course of infantile hemangioendothelioma (Dachman et al.).

Pathogenesis. Most infantile hemangioendotheliomas are multinodular, involve distant organs (such as the skin), and are diagnosed by age 8 months. Furthermore, many infants with infantile hemangioendothelioma are born prematurely and may have other congenital anomalies. Although most lesions involute spontaneously, a rare lesion may demonstrate malignant behavior and metastasize. Thus, a neoplastic transformation may occur in what otherwise appears to be a hyperplastic developmental anomaly. Plastic casts of multinodular infantile hemangioendotheliomas demonstrated that the portal veins were the main feeding vessels of the vascular nodules (Othersen and Watanatittan). Although the fetus has a very high portal blood flow compared to the infant, it is curious that the vascular lesions become clinically manifest and grow months after birth when portal blood flow should be "normalized." The stimulus for the abnormal vascular proliferation is unknown because lesions occur in the skin that is removed from the physiologic stimulus of the fetal-related high portal blood flow.

Gross. Infantile hemangioendotheliomas are multiple and diffuse (multinodular type), and one variant is a solitary large lesion. Both lobes are usually involved in the multinodular tumors, while the right lobe is favored in the solitary variant. The nodules vary from a few millimeters to 15 cm and are usually 0.5 to 3 cm in diameter. Larger lesions may be umbilicated. Multinodular diffuse tumors are usually round, sharply defined, red-brown, white, and yellow nodules with central fibrotic areas (figs. 92, 93). Solitary lesions tend to be firm and white with focal hemorrhage (fig. 94). Calcification, hemorrhage or infarction may be present. Dehner (1978) reported no difference in the size of diffuse or solitary types and there is no correlation between heart failure and size of tumor or pattern (solitary vs. multiple nodules).

Microscopic. The microscopic pattern of infantile hemangioendothelioma has been classified into two types (Dehner, 1978), although many patients do not fit easily into one of the two groups. We have had difficulty classifying all areas of each infantile hemangioendothelioma. Type 1, the most common pattern, is an orderly proliferation of small vascular channels lined by cells with an innocuous cytologic appearance (figs. 95, 96). The endothelial cells form a single layer of plump cells with little space for erythrocytes (fig. 97). Bile ducts are scattered among the vascular channels. The center of the lesion may have more cavernous areas, as well as hemorrhage, thrombosis, fibrosis, and calcification (fig. 95). Cavernous areas are noted in approximately one-half of the patients and correlate with the "puddling" noted in the capillary phase of the angiogram. No Kupffer cells are noted and by hepatic scintigraphy, the lesions are "cold" (Stanley et al., 1977). The type 1 lesions appear centered around portal tracts and grow by expansion, although some areas have infiltration of adjacent sinusoids (fig. 98). Solid growth of vessels results in little visible blood (fig. 96). Large vascular channels with multilayered endothelial cells and fibrous stroma are often noted (figs. 99, 100). Type 2 infantile hemangioendothelioma has endothelial cells with more hyperchromatic nuclei, more pleomorphism, and, often, multilayered lining, as well as irregular budding, branching, and mitosis. Fibrosis occurs in the older lesion (age 6-8 months or more). A rare lesion shows aggressive malignant behavior and has highly atypical features, such as large nuclei (figs. 101, 102). Infantile hemangioendothelioma lacks sharp demarcation from the liver cords and the vascular proliferation often extends into the cords (fig. 98), but infiltration by small nests into the middle of the lobule and vein invasion are features of malignant hemangioendothelioma (fig. 103). The cutaneous lesion has similar histologic changes and is not evidence of metastasis (figs. 90, 91).

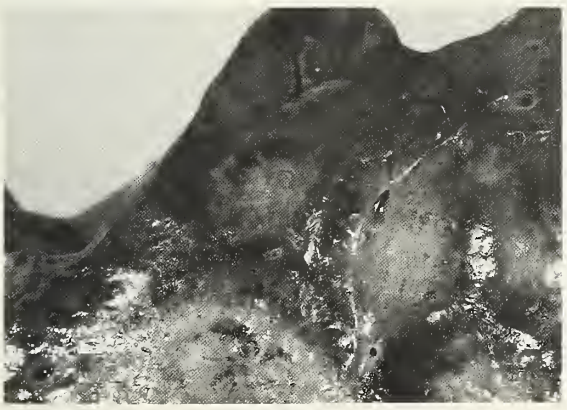


Figure 92
INFANTILE HEMANGIOENDOTHELIOMA
The external liver surface reveals bulging nodules. The central white areas are indicative of fibrosis.

Figure 93
(Figures 93, 97, and 98 are from the same patient)
INFANTILE HEMANGIOENDOTHELIOMA
Multinodular hemangioendothelioma is seen in this greatly enlarged liver of a 2 month old boy. The cut surface reveals gray-red masses with hemorrhage. (Fig. 111 from Fascicle 25, First Series.)

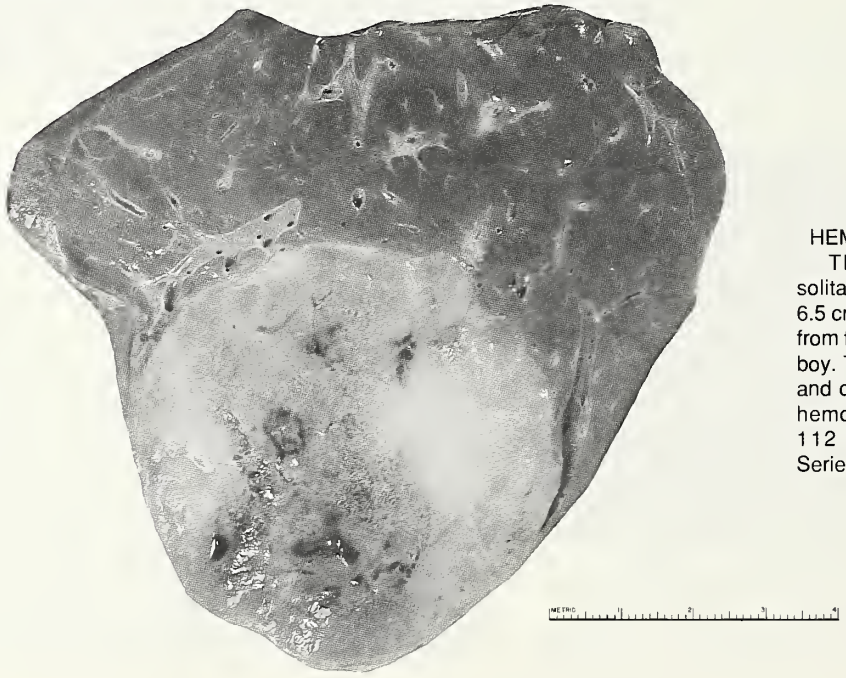


Figure 94
INFANTILE
HEMANGIOENDOTHELIOMA
This encapsulated, large, solitary hemangioendothelioma, 6.5 cm in diameter, was removed from the left lobe of a 10 week old boy. The central area is vascular and cavernous spaces and focal hemorrhage are present. (Fig. 112 from Fascicle 25, First Series.)

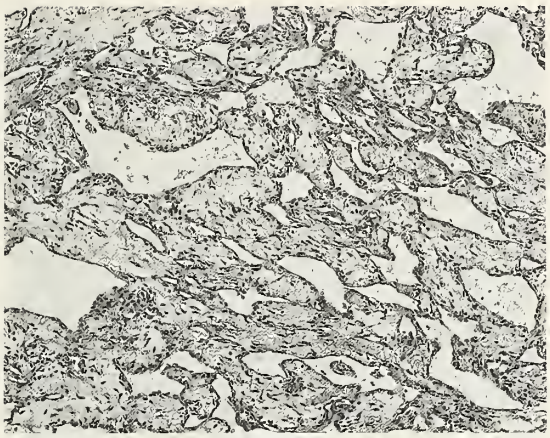


Figure 95
INFANTILE HEMANGIOENDOTHELIOMA
The central cavernous areas of infantile hemangioendothelioma lack the thin walls and incomplete septae noted in the usual adult cavernous hemangioma. X70. (Courtesy of Dr. Paul Potter, Des Moines, Iowa.)

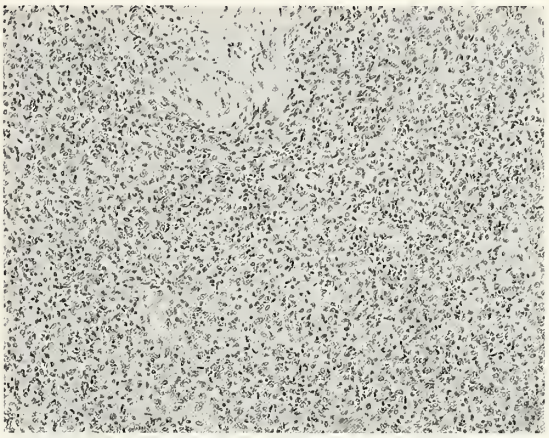


Figure 96
INFANTILE HEMANGIOENDOTHELIOMA
This area of infantile hemangioendothelioma has solid growth of endothelial cells, with little space for blood. It was an excision biopsy of a 5 ½ month old girl. X85. (Courtesy of Dr. Bruce Beckwith, Seattle, Washington.)

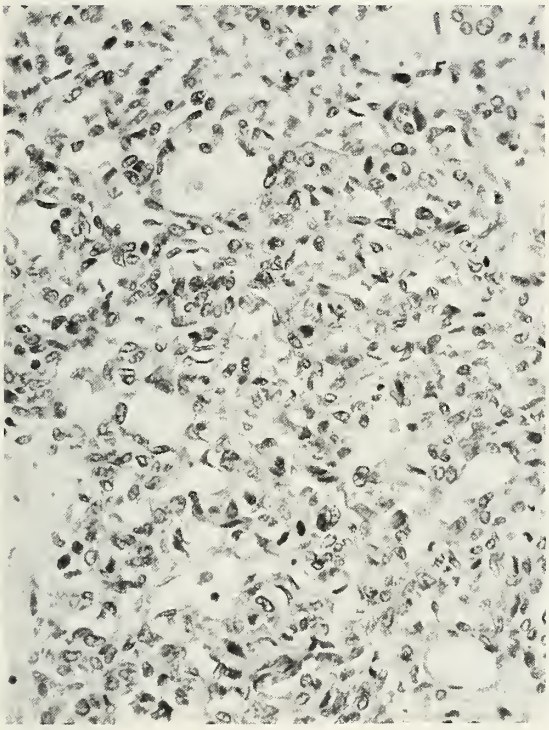


Figure 97
INFANTILE HEMANGIOENDOTHELIOMA
Plump endothelial cells fill the vascular channels and account for the firm and fibrous texture of part of the nodule noted in Figure 94. X200. (Fig. 113 from Fascicle 25, First Series.)

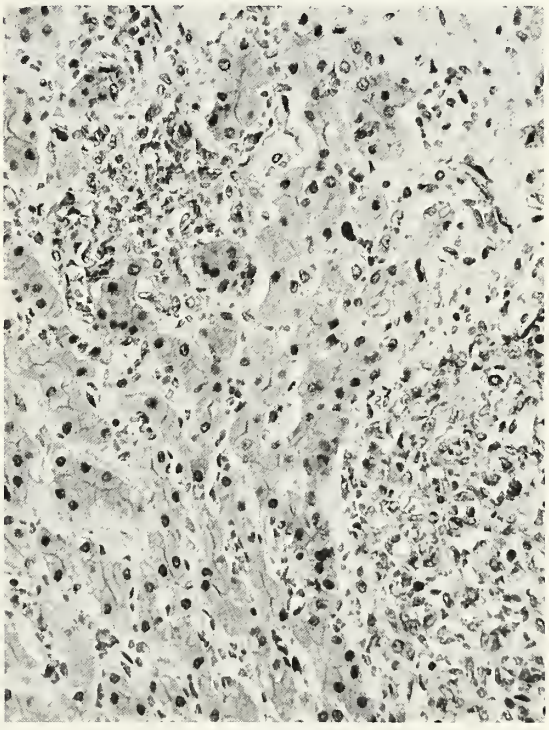


Figure 98
INFANTILE HEMANGIOENDOTHELIOMA
Infantile hemangioendothelioma growth patterns include a solid bulging nodule (lower right) as well as an infiltrative pattern (upper left) that grow into the sinusoids. X220. (Fig. 114 from Fascicle 25, First Series.)

Figure 99
(Figures 99 and 100 are from the same patient)
INFANTILE HEMANGIOENDOTHELIOMA
Both large and small vascular channels have thickened walls and multiple layers of endothelial cells. X120. (Fig. 115 from Fascicle 25, First Series.)

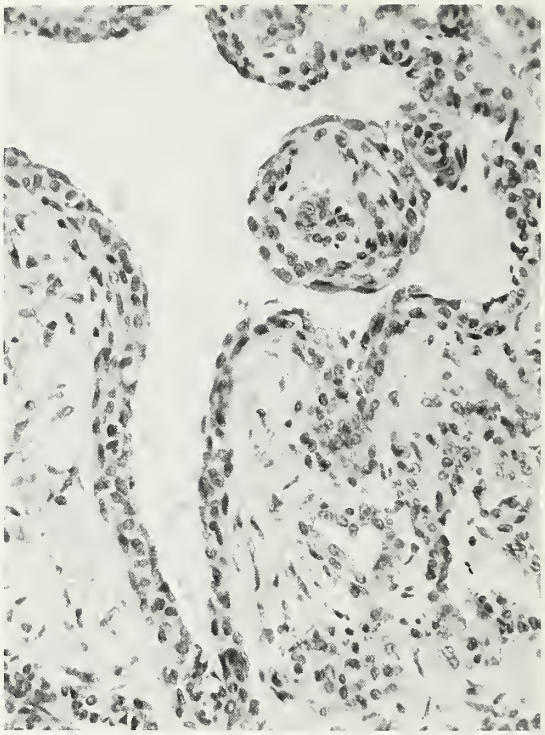


Figure 100
INFANTILE HEMANGIOENDOTHELIOMA
Papillary growth of endothelial cells within a vascular lumen is noted in same patient shown in figure 99. X320. (Fig. 116 from Fascicle 25, First Series.)

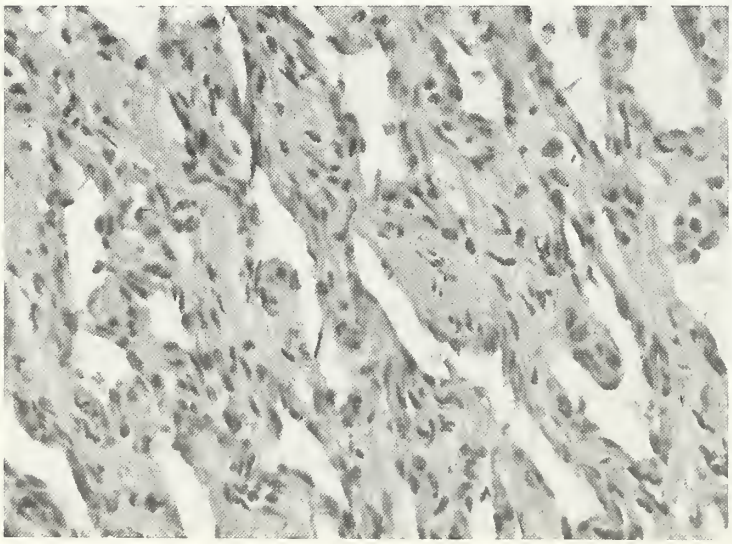


Figure 101
(Figures 101-103
are from the same patient)
INFANTILE HEMANGIOENDOTHELIOMA
This 6 month old girl had numerous hepatic nodules. One was biopsied and demonstrated typical infantile hemangioendothelioma with thin endothelial lining of small cells lacking cytologic atypia. X1240. (Courtesy of Dr. William Hartmann, Nashville, Tennessee.)

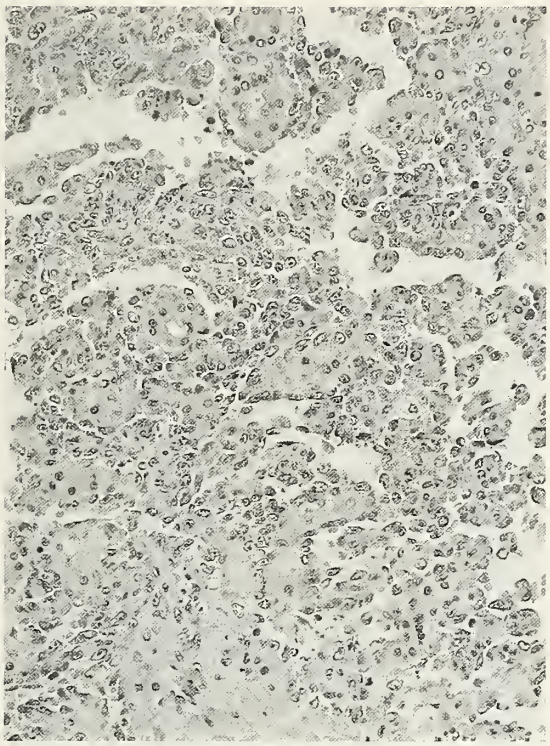


Figure 102
INFANTILE HEMANGIOENDOTHELIOMA
Malignant hemangioendothelioma (overt hepatic angiosarcoma) developed in the patient shown in figure 101. The infant was given steroid medication. At the age of 3 years she developed hepatomegaly and a large left lobe was resected that contained many large hemorrhagic nodules. Broad sheets of oval, polygonal, basophilic cells with scattered fibrous stroma, large areas of hemorrhage, and necrosis were present. The patient is alive and well 10 years later. X310. (Courtesy of Dr. William Hartmann, Nashville, Tennessee.)

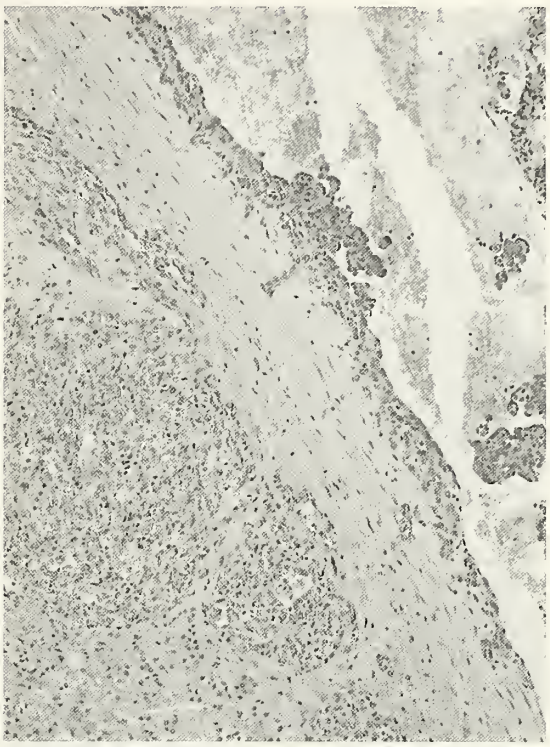


Figure 103
INFANTILE HEMANGIOENDOTHELIOMA
Major vein invasion and growth of malignant hemangioendothelioma is noted. X620. (Courtesy of Dr. William Hartmann, Nashville, Tennessee.)

Variants. Solitary infantile hemangioendothelioma has similar histologic and clinical features, except skin angiomata are absent. The large lesion can be resected if well-circumscribed, in contrast to multinodular lesions which cannot be excised.

Differential Diagnosis. Many lesions are not easily separated into type 1 or type 2 infantile hemangioendotheliomas, with some areas of type 2 present in a tumor that is otherwise predominantly type 1. Cavernous hemangioma occurs in the same young age group, but is usually an incidental finding. Cavernous hemangioma is distinguished by the absence of typical type 1 areas and by the single layer of mature, flat, endothelial cells on stroma that is mature fibrous tissue rather than myxoid stroma with small bile ducts, as in infantile hemangioendothelioma. Hemangiosarcoma of the adult has some similar histologic features to type 2 infantile hemangioendothelioma, such as invasive qualities of growth within portal vessels and within the hepatic parenchyma,

hyperchromatic nuclei, and mitosis, but type 2 infantile hemangioendothelioma also includes remnants of portal areas. The solid areas of angiosarcoma usually lack portal areas and are large fields of spindle cells with angulated, enlarged nuclei within the vascular channels. A third diagnostic consideration is mesenchymal hamartoma, which also frequently has prominent endothelial proliferation and small vascular channels. However, mesenchymal hamartoma has a variable pattern of edematous myxoid stroma that separates the vessels and contains bile ducts, and the large tumor has grossly apparent cystic spaces which are lacking in infantile hemangioendothelioma.

Prognosis. Congestive heart failure requires vigorous medical treatment. Specific treatment of the hepatic lesion requires resection of solitary lesions, hepatic artery ligation, and corticosteroids for multifocal lesions (Vorse et al.). Radiation therapy has also been successful. Therapeutic embolization with polyvinyl alcohol has been reported (Stanley et al., 1983). If no or mild clinical symptoms are noted, then no treatment is provided and spontaneous involution usually begins at 6 to 8 months (Dachman et al.; Lucaya et al.). The prognosis is good if there are no symptoms. Metastasis occurred in one patient of the type 2 infantile hemangioendothelioma in the series of Dehner and Ishak.

LYMPHANGIOMATOSIS

SYNONYMS AND RELATED TERMS: Lymphangioma; hemolymphangioma.

Definition. Hepatic lymphangiomatosis is the presence of either solitary, massive, or multiple masses composed of prominent, dilated, lymphatic channels that distort the normal hepatic architecture by "compressing" the hepatocytes. The dilated channels may contain blood. An endothelial lining is present, but the nuclei are not prominent. The systemic form involves other organs, including the skeleton, lymph nodes, soft tissue, and retroperitoneum. One variant is limited to the liver either as a solitary, massive lesion or as multiple nodules.

Incidence. Both localized and diffuse lymphangiomatosis are very rare with only a few known patients (one reported in the literature and three others in our files).

Clinical. The systemic form often occurs in children and the liver may be markedly enlarged (Asch et al.). Systemic lymphangiomatosis has a poor prognosis, especially if the bones are involved, whereas the "hepatic only" variant has not been fatal and has occurred in adults. There are three examples of the localized "hepatic only" lymphangioma in adult men (ages 32, 49, and 50 years). An asymptomatic abdominal mass was detected, which led to biopsy or surgery.

Pathogenesis. A congenital anomaly of the lymphatic system is suggested by the occurrence in childhood and systemic locations. The solitary massive lesion limited to the liver in adults is of uncertain etiology.

Pathology. In one report, the diffuse form was multiple cysts with thick, fibrous walls that were focally calcified. The cyst contents ranged from serous fluid to bloody fluid (Asch et al.). The cystic tumors occupied 60 percent of the liver and large areas of the spleen (fig. 104). In three adult men with the solitary variant, the liver was massive; the largest was 7620 g (29x20x20 cm). No cysts were visible on the cut surface (pl. IV-B). One patient with

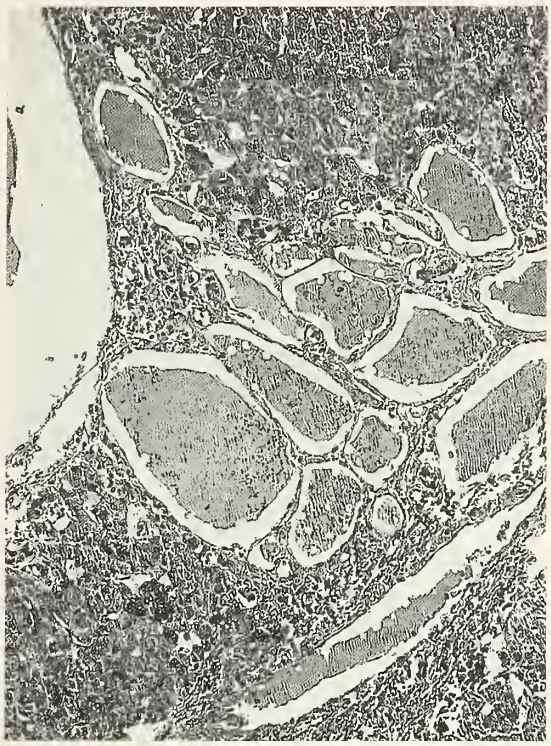


Figure 104
LYMPHANGIOMATOSIS
Diffuse lymphangiomatosis involves portal areas with cavernous channels lined by endothelium and normal hepatic cords. X250. (Courtesy of Dr. Arthur H. Cohen, San Pedro, California.)

histologic features of the solitary type had several large foci involving both lobes (Van Steenbergen et al.). Microscopic features are distinctive, with the systemic type having portal areas containing numerous cystic spaces filled with pink fluid (fig. 104). The cyst lining is flattened endothelium. The hepatic variant has marked widening of the sinusoids with atrophy of the hepatocyte cords (figs. 105, 106). A thin, fibrillar matrix is present in the sinusoids. Factor VIII staining of the fibrillar lining is negative in our laboratory, but Van Steenbergen and associates reported a positive reaction. A thin capsule separates the tumor from the adjacent liver and no infiltration of the sinusoidal change is noted (fig. 107).

Differential Diagnosis. The hepatic form is recognizable as a large tumor and the presence of hepatocytes in cords may suggest a primary epithelial tumor. However, the hepatocytes are atrophic and have no cytologic atypia. Cavernous hemangioma appears similar by gross examination, but the lymphangioma is less bloody and the microscopic features reveal scanty endothelial cells and fibrous stroma, as noted in hemangioma.

LIPOMA

Definition. Benign hepatic tumors composed of fat cells include lipoma (pure type); hibernoma (composed of a distinctive fat cell); and the combined types, angiolipoma with vascular components, angiomyolipoma with smooth muscle components, and myelolipoma with hematopoiesis.

Incidence. These tumors are uncommon and are usually reported individually. Four benign fatty tumors were reviewed by Ishak in 1976 and a larger series of 12 were reported by Goodman and Ishak in 1984. As more detailed radiographic examination is completed (with CT scans and MRI), the true incidence of lipoma will likely become greater.

Clinical. These tumors are not usually clinically manifest and are incidental findings. No sex predilection is noted and the age range is broad (24-70 years). Up to 10 percent of patients with renal angiomyolipoma have associated hepatic fatty tumor (either lipoma or angiomyolipoma), and many also have tuberous sclerosis (Ramchand et al.; Roberts et al.).

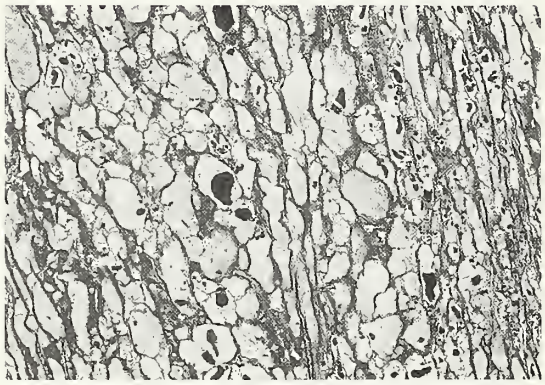


Figure 105
(Figures 105-107 and Plate IV-B
are from the same patient)
LYMPHANGIOMATOSIS
Within the lymphangioma there are markedly dilated sinusoidal spaces with pink fluid and thin hepatic cords. X210. (Courtesy of Dr. Daniel de la Vega, San Diego, California.)

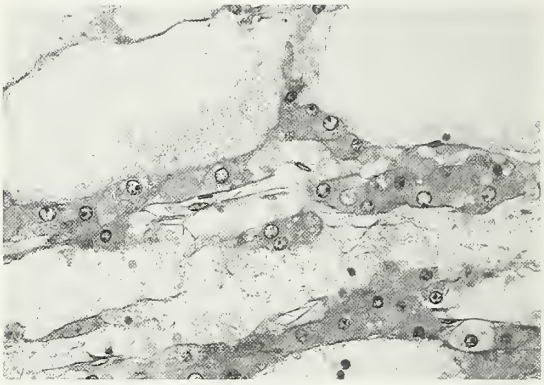


Figure 106
LYMPHANGIOMATOSIS
The hepatic lymphangioma has atrophic hepatocytes with small nuclei, scanty pink cytoplasm, and thin fibrils within the sinusoids. Very few sinusoidal cell nuclei are present. X840. (Courtesy of Dr. Daniel de la Vega, San Diego, California.)

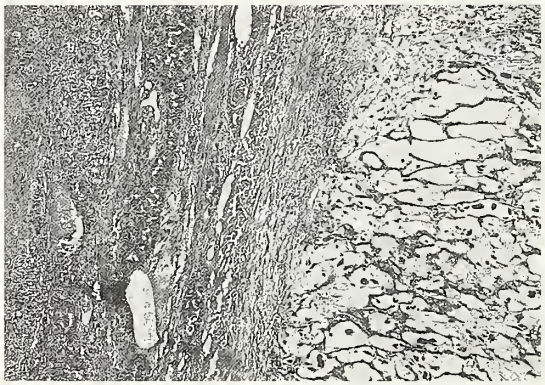


Figure 107
LYMPHANGIOMATOSIS
A fibrous capsule separates the compressed adjacent liver from the lymphangioma. X85. (Courtesy of Dr. Daniel de la Vega, San Diego, California.)

Pathology. Multiple large tumors are reported (Ishak). They are usually solitary, well-circumscribed, round, lack a capsule, usually occur in noncirrhotic liver, range in size from 1 to 20 cm in diameter, and may be pedunculated (figs. 108, 109). The microscopic features are similar to lipomatous tumors in soft tissue. In pure lipoma, the tumor is only fat cells (fig. 110). The border of lipoma with liver is relatively sharp. Smooth muscle cells, blood vessels often with thickened walls, and lipocytes of varying size and degree of vacuolization comprise angiomyolipoma (figs. 111-113). Hibernoma may show transition of large vacuolated adipose cells to a foamy, granular, brown fat cell, and focal calcification occurs as distinct round bodies (fig. 114). Incomplete resection of an angiolipoma led to fat necrosis; subsequent resection showed numerous macrophages that resembled hibernoma cells due to the fine granular cytoplasm (fig. 115).

Differential Diagnosis. Pseudolipoma is a consideration if it is well-encapsulated by fibrous tissue and located on Glisson's capsule (fig. 116) (Karhunen, 1985). These pseudolipomatous lesions are probably due to adhesion of colonic appendix epiploic to the hepatic surface. Focal fatty hepatocellular change detected by radiography and ultrasound may appear similar to lipoma; however, histologic examination reveals hepatocytes with fat vacuoles within the cytoplasm and not true lipocytes.

Prognosis. Resection of solitary angiomyolipoma may be necessary to prove the diagnosis or to remove a large tumor, but no malignant transformation is known (Kawarda and Mizumoto; Peters et al.).

Figure 108
(Figures 108 and 110 are from the same patient)
LIPOMA

This 54 year old woman had a round, well-circumscribed lipoma of the right lobe of the liver that measured 2 cm in diameter. (Fig. 117 from Fascicle 25, First Series.)

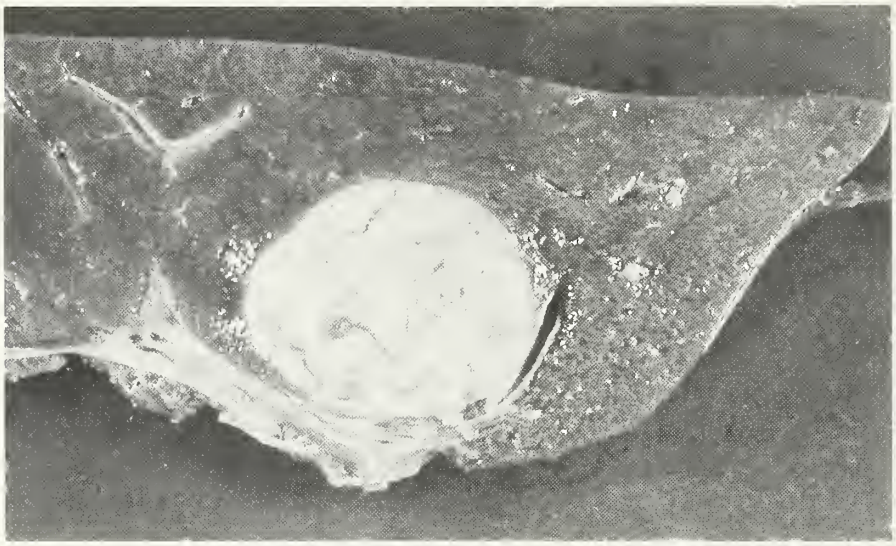


Figure 109
(Figures 109, 111, and 112 are from the same patient)
ANGIOMYOLIPOMA
Angiomyolipoma in a 59 year old woman was 4.7x3x3 cm in size, golden-yellow, and well-circumscribed and was detected by ultrasound in the right lobe and surgically removed. (Courtesy of Dr. Y. Kawarda, Tsu-City, Mie, Japan.)

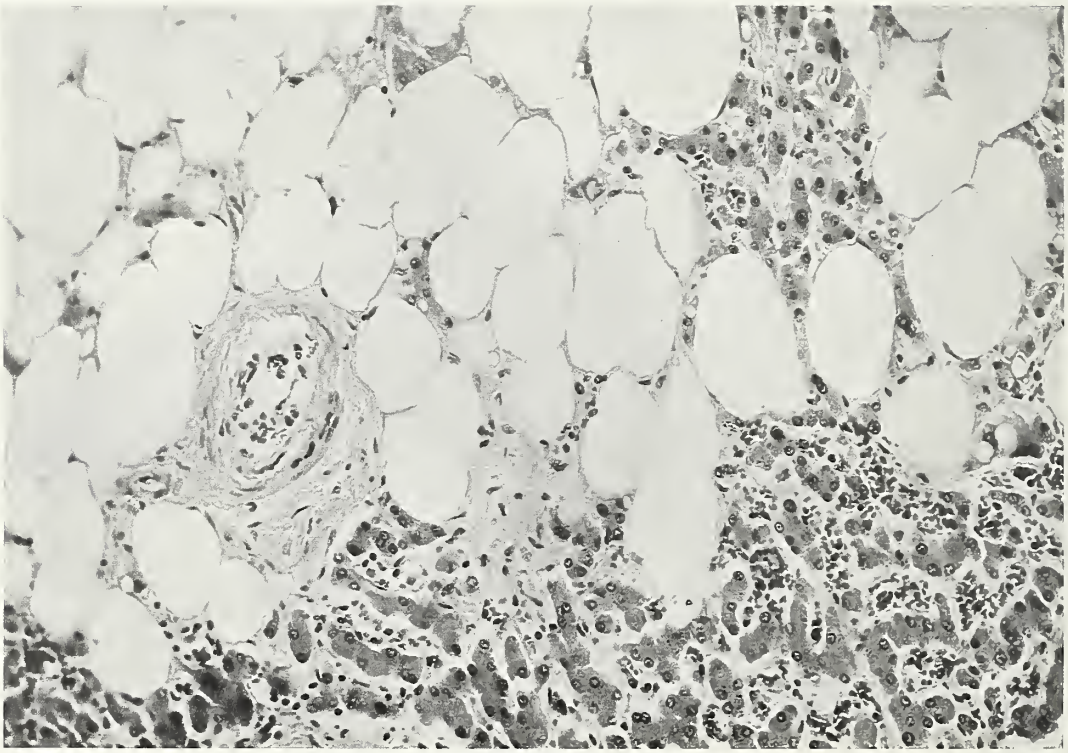


Figure 110
LIPOMA
The margin of lipoma with normal liver is fairly abrupt with only a few lipocytes extending into the adjacent hepatic parenchyma. X135. (Fig. 118 from Fascicle 25, First Series.)

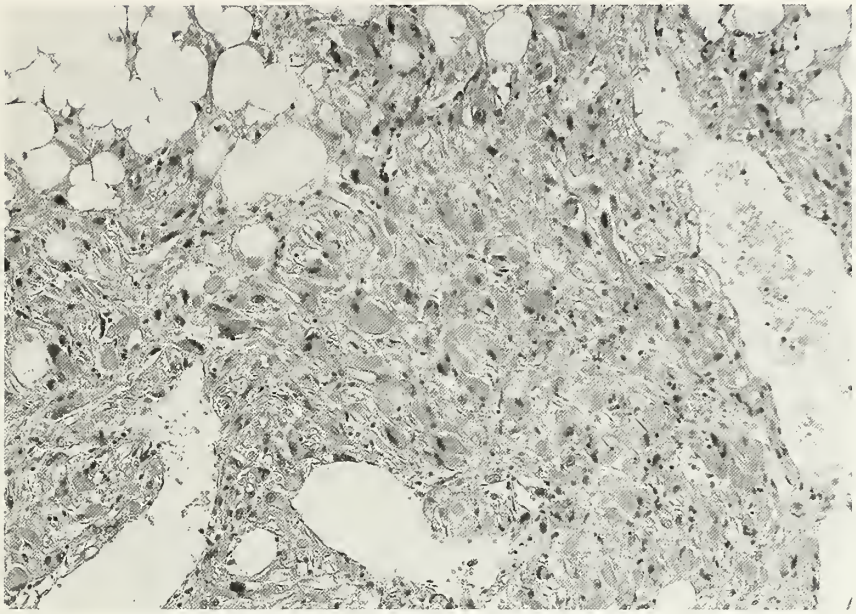


Figure 111
ANGIOMYOLIPOMA
The angiomyolipoma has a mixture of mature lipocytes, abundant small vessels, and foci of smooth muscle cells. X100. (Courtesy of Dr. Y. Kawarda, Tsu-City, Mie, Japan.)

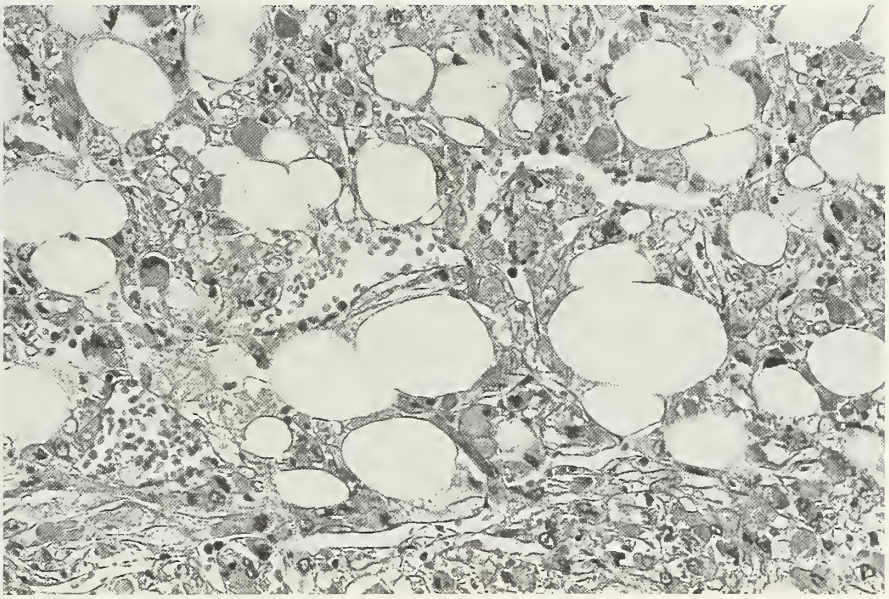


Figure 112
ANGIOMYOLIPOMA
This angiomyolipoma has clusters of smooth muscle cells and fat intermixed. X100. (Courtesy of Dr. Y. Kawarda, Tsu-City, Mie, Japan.)

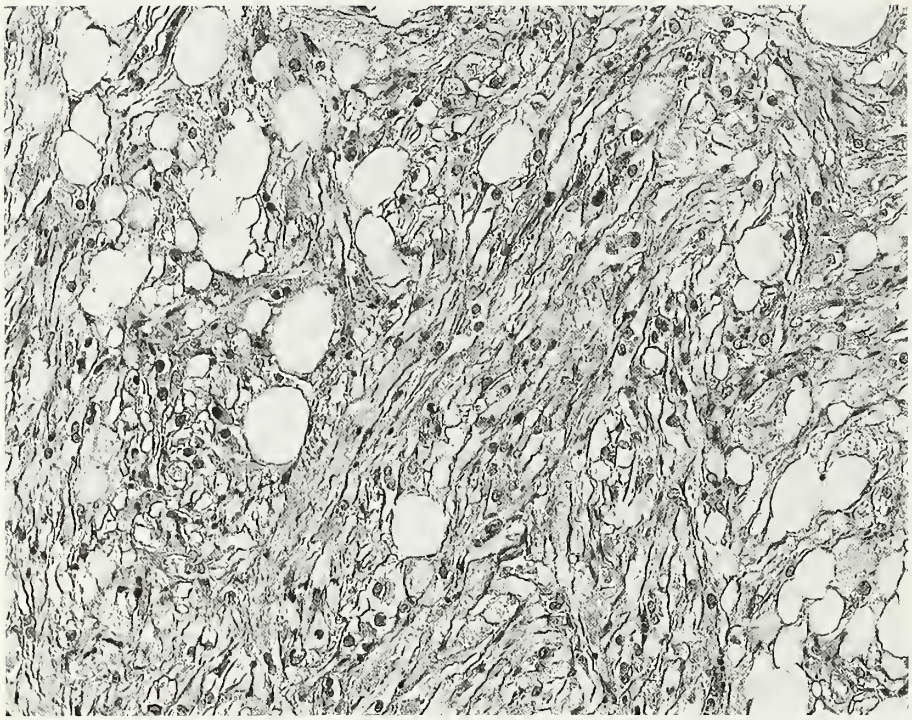


Figure 113
ANGIOMYOLIPOMA
Angiomyolipoma has lipocytes with varying degrees of vacuolization. X200. (Courtesy of Dr. Y. Kawarda, Tsu-City, Mie, Japan.)

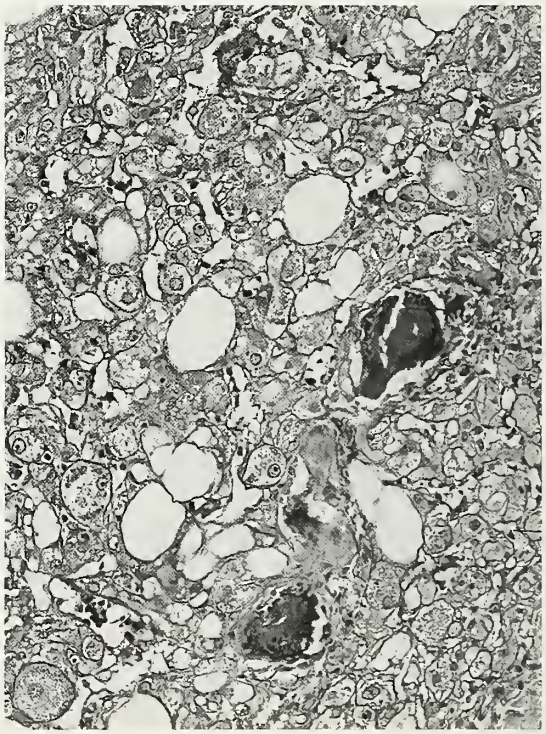


Figure 114
HIBERNOMA
Angiolipoma with hibernoma area contains focal calcification in a 39 year old woman with two resected fatty tumors; a pedunculated, encapsulated, 8x6x5 cm, gritty mass and a separate encapsulated, yellow, 8x6x6 cm mass with a greasy cut surface. X310. (Case 4 from Ishak, K.G. Mesenchymal Tumors of the Liver. In: Hepatocellular Carcinoma. Okuda, K. and Peters, R.L. [Eds.]. New York: John Wiley & Sons, 1976.)

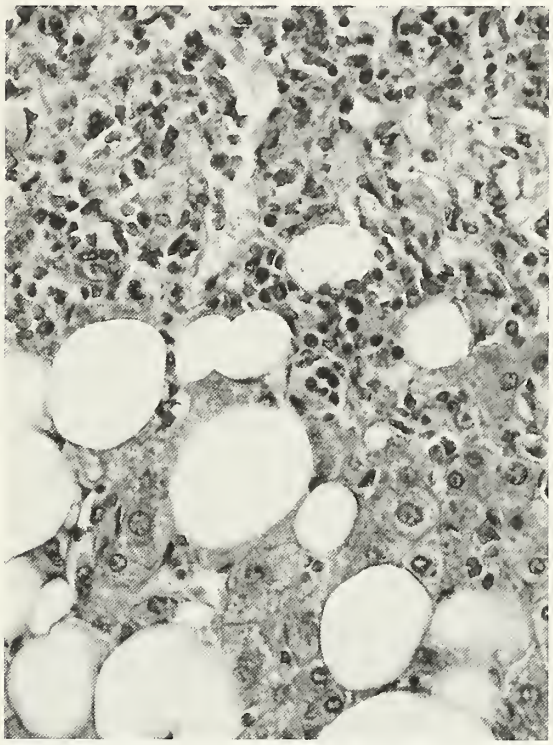


Figure 115
MYELOLIPOMA

A 54 year old woman with myelolipoma had recurrent right upper quadrant abdominal pain. CT scan showed a large hepatic fatty tumor in the posterior right lobe of the liver. A partial resection was completed, but recurrent symptoms led to additional resection of a subserosal, hemorrhagic, necrotic, 8x5x4 cm mass. Within the benign fatty tissue are islands of hematopoiesis and other areas of hemorrhagic and fat necrosis with foamy macrophages. The adjacent liver was not well-demarcated in all areas from the fatty tumor. X1240. (Courtesy of Dr. James Wilkerson, Birmingham, Alabama.)

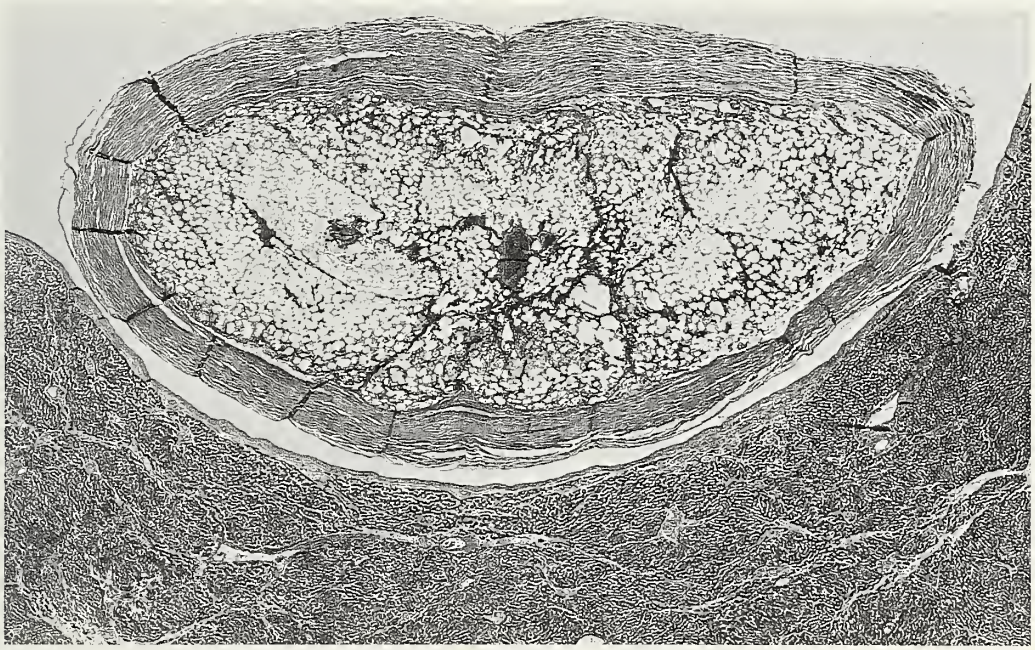


Figure 116
PSEUDOLIPOMA

Pseudolipoma has a thick capsule surrounding fatty lobules and no distinct connection of fat to hepatic parenchyma. X14. (Fig. 205 from Fascicle 25, First Series.)

LEIOMYOMA

Definition. Hepatic leiomyoma is a well-circumscribed, benign, smooth muscle tumor arising in the liver.

Incidence. Hepatic leiomyoma is an extremely rare tumor. There are only four reported cases (Hawkins et al.; Ishak).

Clinical. Cases include two females and one male aged 42, 66, and 87 years old and an epithelioid leiomyoma in a 64 year old man. Vague abdominal symptoms related to a mass lesion may be noted.

Pathology. The solitary tumor is large, well-circumscribed, and lacks hemorrhage or necrosis (fig. 117). The whorled cut surface resembles leiomyoma noted in other locations. Light microscopy reveals interlacing bundles of uniform spindle cells with plump, oval, blund-ended nuclei and no mitosis (figs. 118, 119). Mild variation in cellularity occurs and ultrastructural features include filaments, dense bodies, and a few pinocytotic vesicles (Hawkins et al.). An epithelioid leiomyoma has both typical leiomyomatous areas and plump spindle cells arranged in small nests (fig. 120). Proof of smooth muscle origin is needed. Immunohistochemical stains are useful only in excluding other spindle cell tumors.

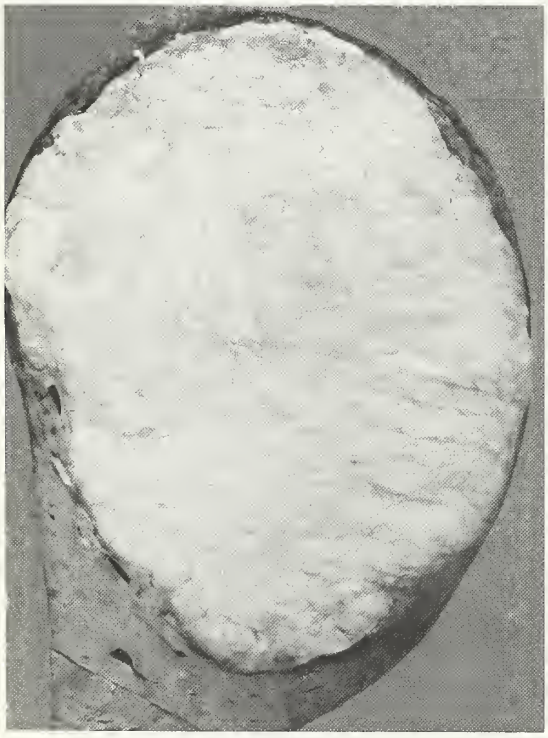


Figure 117
(Figures 117-119 are from the same patient)
LEIOMYOMA
This 1070 g leiomyoma was resected from the left lobe of the liver in a 66 year old man. (Courtesy of Drs. E.P. Hawkins and M.G. McGavern, Houston, Texas.)

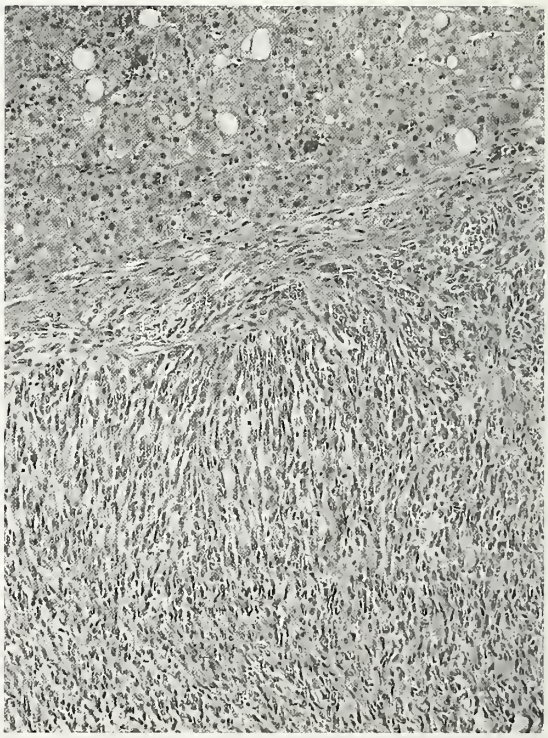


Figure 118
LEIOMYOMA
The hepatic leiomyoma has a sharp margin with the normal liver. A thin fibrous capsule is present in most other areas of the tumor. X310. (Courtesy of Drs. E.P. Hawkins and M.G. McGavern, Houston, Texas.)

Figure 119
LEIOMYOMA
A less cellular area of bland spindle cells has no mitosis in this leiomyoma. X620. (Courtesy of Drs. E.P. Hawkins and M.G. McGavern, Houston, Texas.)

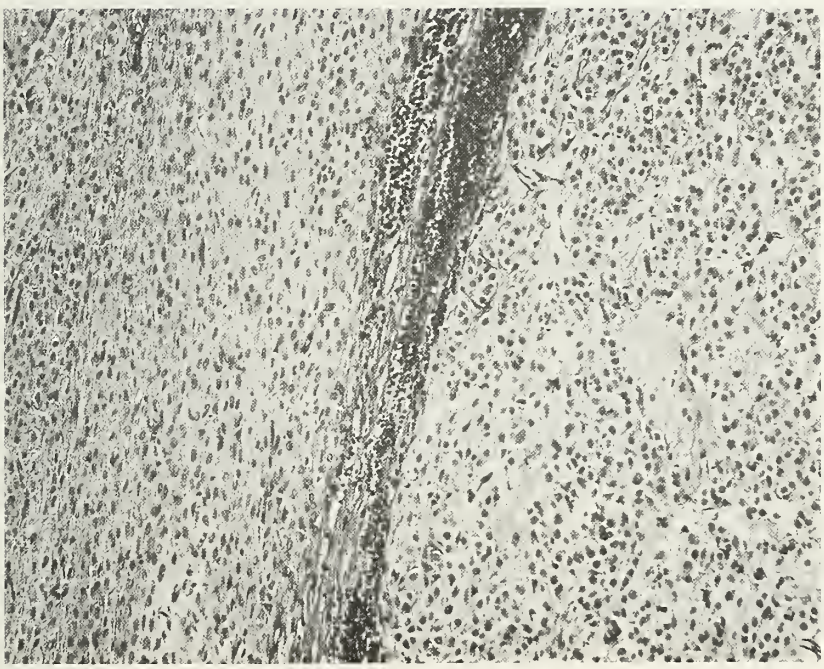


Figure 120
EPITHELIOID LEIOMYOMA
This epithelioid leiomyoma of the liver in a 64 year old man with a 15 cm in diameter, pedunculated right lobe tumor has both typical leiomyomatous cells (left) and rounded, polygonal cells in nests (right) of the epithelioid cells. X120. (Fig. 22 from Ishak, K.G. Mesenchymal Tumors of the Liver. In: Hepatocellular Carcinoma. Okuda, K. and Peters, R.L. [Eds.]. New York: John Wiley & Sons, 1976.)

Differential Diagnosis. The major diagnostic considerations of hepatic leiomyoma are solitary fibrous mesothelioma (fibroma), inflammatory myofibroblastic tumor, malignant fibrous histiocytoma, and hepatic leiomyosarcoma, as well as metastatic leiomyosarcoma. Solitary fibrous mesothelioma (fibroma) is distinguished by its usual connection to the capsule; prominent intermixing of thick, fibrous, collagenous fibers; spindle cells with tapered nuclei; and a lack of filamentous elements by electron microscopy. Inflammatory myofibroblastic tumor has prominent inflammatory cells (lymphocytes and polymorphonuclear neutrophils) admixed with the spindle cells, which also are bland, but often the stroma is edematous. Malignant fibrous histiocytoma is distinguished by mitosis and bizarre and pleomorphic small spindle cells. Hepatic leiomyosarcoma, far more common than leiomyoma, is distinguished by large size, greater cellularity, mitosis, and often necrosis. However, the accurate classification of smooth muscle tumors as either benign or malignant is difficult due to limited experience, limited sampling of the tumors, and limited follow-up information of the few available cases for study. Immunoperoxidase stains have no demonstrated diagnostic value in separating the spindle cell tumors of smooth muscle origin from fibroblastic origin.

FIBROMA

SYNONYMS AND RELATED TERMS: Solitary fibrous mesothelioma.

Solitary fibrous tumors of the liver have been reported under a variety of names including fibroma, fibrosarcoma, solitary fibrous mesothelioma, and extra-ovarian fibrothecoma (Nevius and Friedman). Some reported leiomyoma, leiomyosarcoma, and fibrosarcoma may be fibroma, as no mitosis or metastasis were documented in the bland spindle cell tumors (Gen et al.). Accurate classification has been difficult due to the rarity of the tumors, variation in histologic appearance rather than a distinctive single pattern, and because few tumors have been studied by immunoperoxidase.

Definition. Hepatic fibroma is a large, multinodular, benign, spindle cell tumor. It resembles solitary pleural fibrous mesothelioma, with a variety of histologic appearances ranging from very bland and acellular to whorled spindle cells that may be confused with sarcoma.

Incidence. Hepatic fibromas are rare. We have four cases in our consultation files, two of which Ishak included in the series of benign mesenchymal tumors reported in 1976.

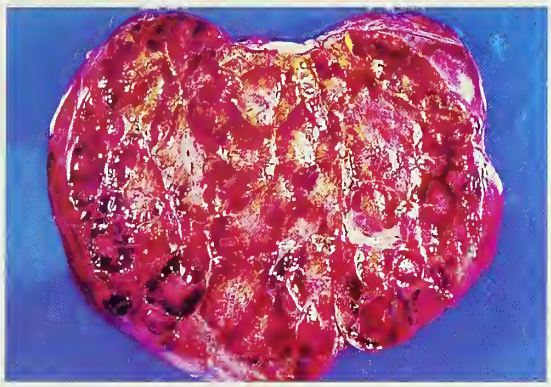
Clinical. The ages of the patients were 21, 27, 78, and 78 years; three of the four patients were women. The large tumors produced mild abdominal discomfort. No recurrence of resected tumor is known.

Pathogenesis. There is no information available regarding association with asbestosis or other environmental factors.

Gross. The large tumors were 860 g (pedunculated), 3800 g, and 4500 g; the largest measured 27x23x15 cm. The external surface was nodular and the cut surface was composed of whorls of fibrous, white tissue with central necrosis; two had "cysts" whereas the third was solid (pl. IV-C). Fibrous bands separated the 0.4 to 8.0 cm nodules.

Microscopic. Microscopic features are variable and include solid, bland, fibrous tissue; variegated, fibrous, collagenous

PLATE IV



A. MIXED CAVERNOUS AND CAPILLARY HEMANGIOMA OF THE NEWBORN

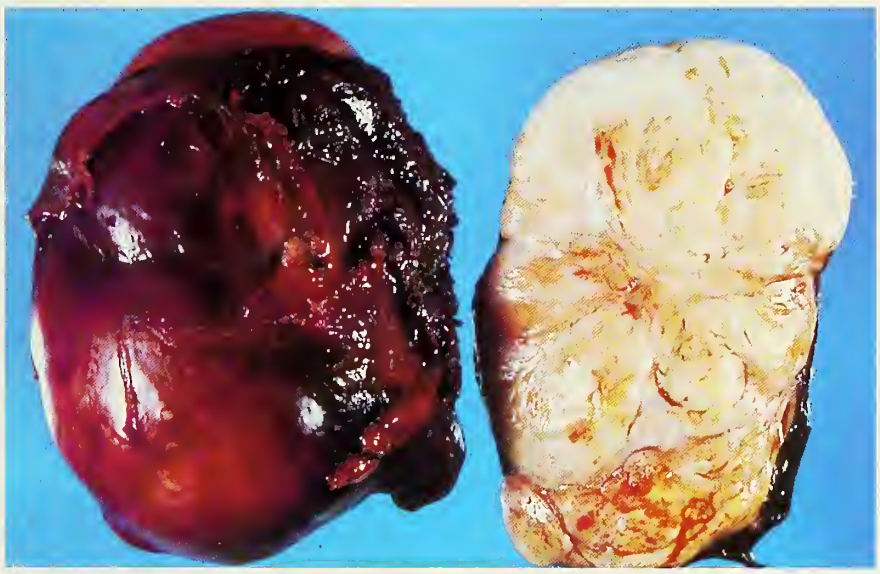
(Plate IV-A and figure 87 are from the same patient)

This female newborn, with massive cavernous hemangioma, died of heart failure at 8 days. (Courtesy of Dr. Al Hirst, Loma Linda, California.)

B. LYMPHANGIOMATOSIS

(Plate IV-B and figures 105-107 are from the same patient)

A 7620 g, solitary, hepatic lymphangioma from a 32 year old man with right lobe resection shows a variegated tan and red cut surface. There was no evidence of recurrence 2 years later and no other organs were involved, as revealed by a CT scan of the abdomen and chest. (Courtesy of Dr. Daniel de la Vega, San Diego, California.)



C. FIBROMA

(Plate IV-C and figure 123 are from the same patient)

The external and cut surfaces of a large, left lobe fibroma of liver resected from an 84 year old woman are illustrated. (Courtesy of Dr. William Hart, Cleveland, Ohio.)

strands with small cells; and more cellular spindle cells with tapered nuclei arranged in bundles. Mitosis is present and the adjacent liver is well-demarcated without invasion of the sinusoids by the fibrous tissue (figs. 121-123). Immunoperoxidase stains demonstrate strong vimentin staining. Kim and Damjanov reported scattered keratin positive cells.

Differential Diagnosis. Distinction of fibroma from fibrosarcoma and leiomyosarcoma may be difficult. The typical fibroma is bland and uniform; increased cellularity, any mitosis, or nuclear pleomorphism are features of sarcoma.

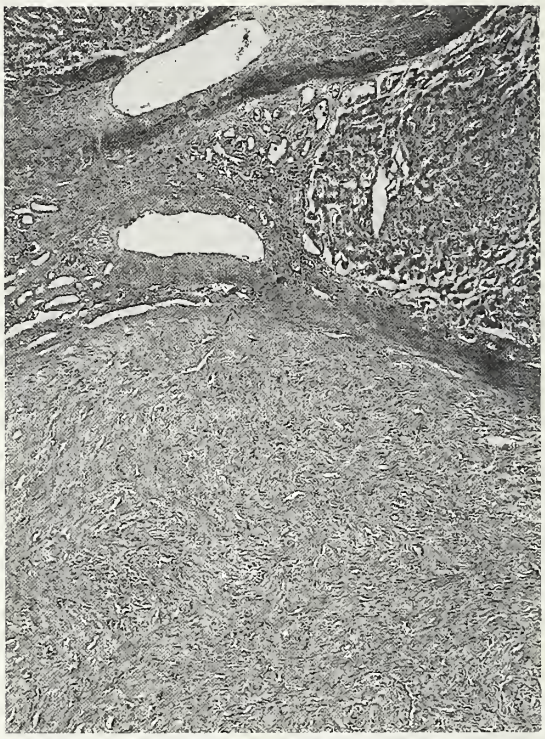


Figure 121
(Figures 121 and 122 are from the same patient)
FIBROMA
Bland, poorly cellular areas predominate in this fibroma which is separated from the normal liver by a capsule. X125. (Courtesy of Dr. H. Kim, Camden, New Jersey.)

INFLAMMATORY MYOFIBROBLASTIC TUMOR (INFLAMMATORY PSEUDOTUMOR)

SYNONYMS AND RELATED TERMS: Post-inflammatory tumor; plasma cell granuloma; inflammatory pseudotumor.

Definition. Inflammatory myofibroblastic tumor is a localized mass composed exclusively of inflammatory cells, fibrosis, macrophages, entrapped hepatic parenchymal elements such as bile ducts and major vessels, and bland spindle cells (myofibroblasts) with oval nuclei lacking both dense chromatin and mitosis. Inflammatory myofibroblastic tumor often mimics a malignant tumor by clinical presentation, gross examination, and histologic features. If an etiology for a solitary hepatic inflammatory mass is identified, such as a healing abscess or post-traumatic injury, then the term inflammatory myofibroblastic tumor does not apply, even though the histologic features may be similar.

Incidence. Inflammatory myofibroblastic tumor is a relatively rare lesion with a few scattered case reports. A large review and an addition of five new patients was published by Anthony and Telesinghe.

Clinical. Inflammatory myofibroblastic tumor is a hepatic mass, usually hilar, and produces no diagnostic clinical or laboratory findings. Fever and leukocytosis are common. Many reported inflammatory myofibroblastic tumors have been in children (Anthony and Telesinghe; Dehner, 1986; Hertzer et al.; Someren).

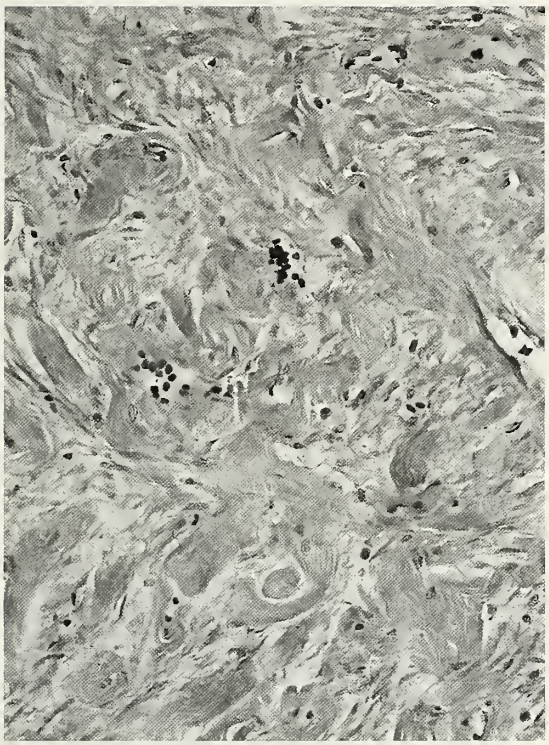


Figure 122
FIBROMA
Thick collagen bands are abundant in some areas of the fibroma. X620. (Courtesy of Dr. H. Kim, Camden, New Jersey.)

Figure 123
(Figure 123 and Plate IV-C are from the same patient)
FIBROMA
Hepatic fibroma may have a variegated appearance produced by thin collagen bands and bland spindle cells. X620. (Courtesy of Dr. William Hart, Cleveland, Ohio.)

Pathogenesis. By definition, recognizable causes of hepatic inflammatory injury that mimic the histologic and clinical features are excluded from this diagnosis. The histologic features are compatible with a vascular mechanism, such as thrombosis and infarction of a major region of the liver. Curiously, the mechanism of injury occurs only once because the lesion is solitary; recurrence is rare, but not unknown (Dehner, 1986). The most common similar lesion is a healing, large, hepatic abscess secondary to a microorganism such as Endamoeba histolytica, or a pyogenic abscess infected by a variety of bacteria. The large size of inflammatory myofibroblastic tumor often is associated with expansion and pressure on adjacent hepatic parenchyma. Consequently, there may be occlusion of major vascular structures and subsequent secondary thrombosis and infarction. However, the primary initiating event is unknown and possibly destroyed by the inflammatory process.

Gross. The several reported cases are remarkable because of their relatively

large size, ranging from a few centimeters to nearly replacing a lobe (usually the right lobe) at 25 cm (Anthony and Telesinghe). Inflammatory myofibroblastic tumor is usually well-circumscribed, but not encapsulated, and the cut surface may be very yellow. The adjacent liver tissue is normal. Lack of traceability to the bile duct or gallbladder exclude bile duct obstruction as a cause for the proliferative process.

Microscopic. The central area is typically composed of dense fibrous tissue (fig. 124) and the margin is composed of spindle cells, foamy histiocytes, abundant lymphocytes, plasma cells, and macrophages (fig. 125). Major bile ducts remain from the collapse and atrophy of hepatic tissue secondary to the expanding lesion. There is a histologic similarity to nodular fasciitis (Chen), and in one case a needle biopsy of a 6 cm mass taken several weeks prior to surgical excision was misinterpreted as sarcoma due to the myxoid stroma and prominent large spindle cells (fig. 126). There is an incomplete fibrous capsule and the border of inflammatory myofibroblastic tumor is vague and indistinct.

Figure 124
(Figures 124 and 125 are from the same patient)
INFLAMMATORY MYOFIBROBLASTIC TUMOR
Inflammatory myofibroblastic tumor may have large fibrous areas with little inflammation resembling fibroma. X310. (Courtesy of Dr. William Hart, Cleveland, Ohio.)

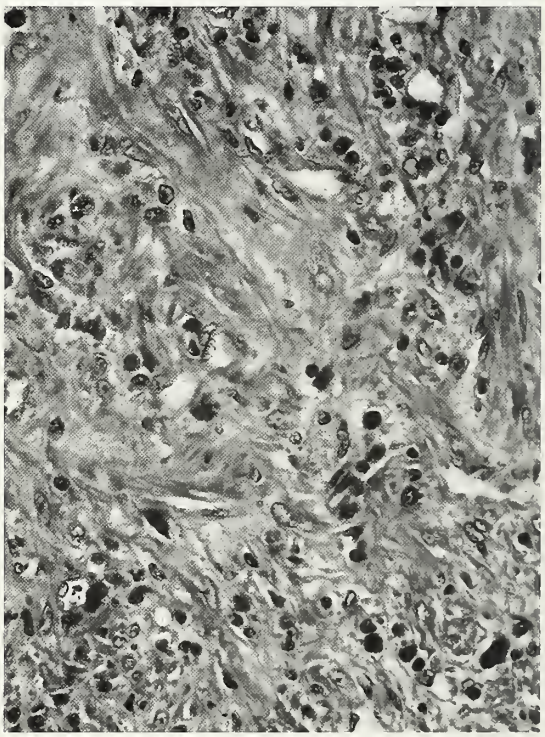


Figure 125
INFLAMMATORY MYOFIBROBLASTIC TUMOR
Inflammatory myofibroblastic tumor typically is composed of a mixture of fibrous tissue, lymphocytes, plasma cells, and reactive, plump spindle cells (myofibroblasts). X1240. (Courtesy of Dr. William Hart, Cleveland, Ohio.)

Differential Diagnosis. Inflammatory myofibroblastic tumor mimics several benign and malignant lesions including a healing abscess, traumatic pseudocyst, lymphoma, and spindle cell sarcoma (especially malignant fibrous histiocytoma). A healing hepatic abscess due to bile duct disease such as calculi, stricture, cholecystitis with adjacent spread of inflammation, or infectious organism such as Endamoeba histolytica, may produce a fibrous hepatic mass. These other diseases must be excluded by culture, clinical history, and bile duct study. Trauma-induced hepatic infarction may progress to pseudocystic liquefied lesions (Henson et al.). Such rare traumatic pseudocysts follow severe abdominal trauma and may be discovered many months after the injury.

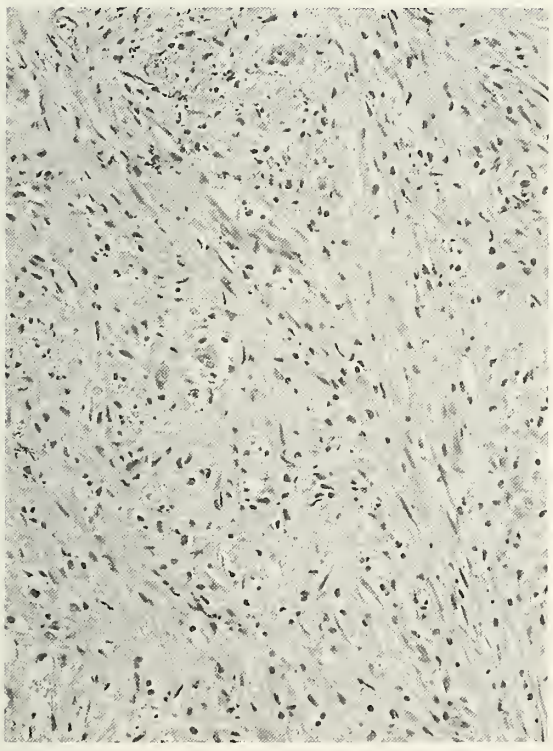


Figure 126
INFLAMMATORY MYOFIBROBLASTIC TUMOR
This needle biopsy of an inflammatory myofibroblastic tumor was taken from a 29 year old man with high fever and chills. The 6 cm in diameter mass was in the right lobe of liver near the gallbladder. The patient improved, but later became ill, which led to resection of the mass. The initial biopsy showed uniform spindle cells without nuclear atypia and no significant inflammation. This needle biopsy was probably not representative because a later specimen had foamy histiocytes and inflammation. X620. (Courtesy of Dr. Karl T.K. Chen, Fresno, California.)

A small biopsy (needle or wedge) of malignant lymphoma or Hodgkin's disease can be difficult to distinguish from inflammatory myofibroblastic tumor because both may be a prominent solitary mass and be composed of lymphocytes and histiocytes. Exclusion of neoplastic hematopoietic neoplasm may require additional tissue and immunohistochemical markers to demonstrate monoclonal lymphocytic proliferation. However, in the presence of lymphoid (germinal) follicles in a hepatic mass, lymphoma is very unlikely. Some very poorly differentiated sarcomas may have moderate fibrosis and lymphocytic infiltration. Malignant fibrous histiocytoma has histologic similarities to inflammatory myofibroblastic tumor, but the pleomorphism of the spindle cells and mitosis are helpful distinguishing features. A small needle biopsy of epithelioid hemangioendothelioma may be difficult to exclude because of the abundant fibrosis and scattered lymphocytes, but a Factor VIII stain will identify the proliferating tumor cells.

Prognosis. The few reported cases reveal resolution of the disease (Chen).

MYXOMA

Definition. Myxoma is a relatively large solitary tumor with edematous, bland, myxoid stroma and no epithelial component.

Incidence. One known hepatic myxoma was reported in 1937 and two were reported in 1977 (Evans and Hoxie; Foster and Berman).

Clinical. The adult myxoma occurred in a 58 year old man with abdominal pain and a large tumor was found almost replacing the left hepatic lobe. At abdominal exploration, a large hepatic cyst apparently had ruptured. At autopsy 4 months later, the left lobe was replaced by a soft, lobulated, gray mass (Evans and Hoxie). Two additional myxomas were reported in a large hepatic tumor series by Foster and Berman. Two children, 6 and 7 years old, had resection of large myxomas; one is alive and well at age 18 years without evidence of tumor, despite incomplete resection 11 years earlier.

Pathogenesis. The origin of myxoma is unknown and there is no association with other mesenchymal components or tumor.

Pathology. The myxoma is a relatively large solitary hepatic mass with a fibrous capsule. The adjacent liver has focal atrophy, apparently from compression by the growing mass, and no hepatic cord invasion is noted. The reported adult myxoma was 2875 g and nearly replaced the left lobe (fig. 127). The myxoid stroma has stellate cells lacking mitosis, bland nuclear features (fig. 128), and a fibrous capsule is present (fig. 129). There is no invasion of the adjacent hepatic cords by the myxoid stroma and no "trapped" hepatic parenchymal elements in the stroma.

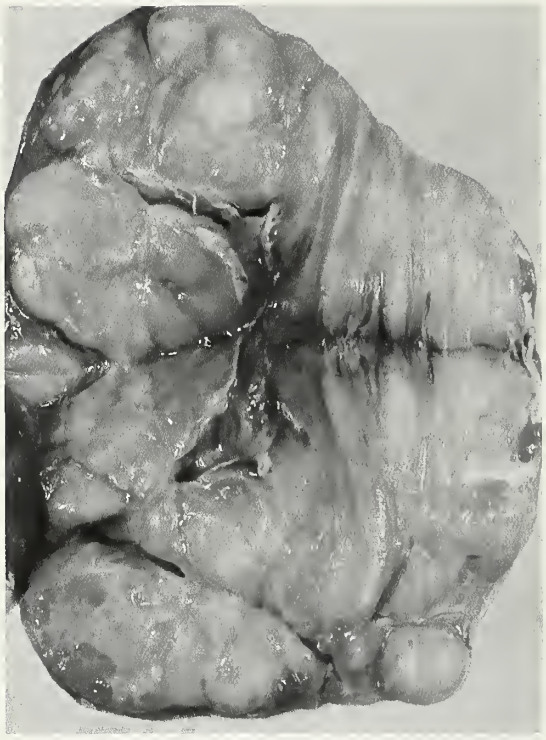


Figure 127
(Figures 127 and 128 are from the same patient)
MYXOMA
A large, multilobulated myxoma of liver shows a cut surface of edematous myxoid stroma and no cysts. (Fig. 123 from Fascicle 25, First Series.)

Differential Diagnosis. Mesenchymal hamartoma is considered if cystic lesions and vascular components are identified. Numerous sections are needed to verify the homogeneity of the tumor, which is expected in myxoma, whereas mesenchymal hamartoma has large cystic spaces, edematous stroma, and many vascular areas as well.

Figure 128
MYXOMA

This myxoma demonstrates the microscopic features of edematous stroma containing few stellate cells with short, plump nuclei lacking mitosis. X135. (Fig. 124 from Fascicle 25, First Series.)

Figure 129
MYXOMA

Compression growth effect on adjacent liver is seen in this myxoma. A fibrous capsule is present. X125. (Courtesy of Dr. MacAdams, Cincinnati, Ohio.)

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TUMORS OF HETEROTOPIC TISSUE AND UNCERTAIN ORIGIN

ADRENAL REST TUMORS

SYNONYMS AND RELATED TERMS: Primary "hypernephroma" of the liver has been applied in the literature, but is not recommended as it refers neither to the origin nor function of the tumor.

Definition. Adrenal rest tumor is derived from misplaced (ectopic) adrenocortical cells within the capsule of the liver. Normally located extrahepatic and perirenal normal adrenal glands must be documented to exclude hepatoadrenal fusion or metastasis from a primary adrenal gland neoplasm. If catecholamine production occurs, the tumor is considered primary hepatic pheochromocytoma. Proof of steroid hormone content or excretion is essential for diagnosis.

Incidence. Functioning adrenal rest tumor is rare and only four case reports were available up to 1986 (Contreras et al.). Hamperl reviewed the literature of 25 cases reported up to 1955 and concluded that none were unequivocal adrenal rest tumors. Most of the earlier reports were probably benign hepatic tumors, such as hepatic adenomas, and some were probably hepatocellular carcinomas (Hamperl).

Clinical. Hormone production by these tumors may produce Cushing's syndrome with amenorrhea, central obesity, fatigue, muscle weakness, moon facies, acne, hirsutism, and weight gain. Blood tests will reveal elevated levels of steroid hormones typical of hypercortisolism. Hepatomegaly may be detected and radiographic studies may reveal a calcified tumor in the liver.

Pathogenesis. Hepatic adrenal rest tumors have been attributed to the dispersal of adrenal primordia, which are thought to involute in the first year. Remnants of adrenal tissue or the entire gland occur beneath the hepatic capsule on the right side. Adrenal hepatic union, observed in five patients, was divided into two categories: adhesion and fusion (Dolan and Janovski). Adrenal hepatic adhesion is recognized by the presence of a thin, connective tissue membrane separating the hepatic parenchyma from the adrenal cortex, which is adherent to the liver. In contrast, adrenal hepatic fusion lacks the separation by fibrous tissue and there is intermingling of the epithelial elements of the two organs (Dolan and Janovski). In several reported patients with hepatic adrenal functioning tumors, a normal right adrenal gland was separate from the liver, thus proving that the tumor did not arise from fusion or adhesion of the liver and normal adrenal (Contreras et al.). The stimulus to promote neoplastic conversion of the ectopic tissue is unknown, and the nontumor adrenal cortical tissue (in normal location) undergoes atrophy.

Gross. The tumor is encapsulated and the cut surface is gray-white to yellow and may contain calcified areas (fig. 130). Wallace and associates reported a patient with a very large right lobe tumor weighing 2600 g. The multinodular tumor, 18x15x15 cm in size, had adrenal rest tissue located in continuity.

Microscopic. Separation of adrenal rest tumor from the normal liver may be a "pushing margin", a thin fibrous capsule or there may be infiltration of the sinusoids by the polygonal small cells (fig. 131). Tumor cells with granular eosinophilic cytoplasm and relatively small nuclei without nucleoli are arranged in broad trabeculae in many

Figure 130
ADRENAL REST TUMOR
This cut surface of a large adrenocortical tumor arising in the liver shows abundant calcification within the encapsulated gray-yellow tumor. (Fig. 15 from Fascicle 25, First Series.)

Figure 131
(Figures 131-135 are from the same patient)
ADRENAL REST TUMOR
A fibrous capsule separates this area of atrophic liver from the androgen-producing tumor (adrenal rest tumor). In other areas, the tumor infiltrates the adjacent sinusoids. X125. (Courtesy of Dr. Albert Stanek, Brooklyn, New York.)

areas (figs. 132, 133), yet other fields have marked pleomorphism of cells and clear cytoplasm (figs. 134-136). Ectopic adrenal rest tissue may be noted at the margin of the tumor (Contreras et al.).

Differential Diagnosis. Metastatic adrenal cortical carcinoma requires identification of nontumor, intact adrenal glands. The microtrabecular growth pattern with sinusoidal lining cells simulates hepatocellular carcinoma, but the lack of nucleoli, the lack of bile production, and the moderate pleomorphism are unlike hepatocellular carcinoma. Metastatic melanoma has similar histologic features that may be difficult to distinguish.

Prognosis. Surgical excision may be curative, but large tumor size may be evidence that the lesion is carcinoma and thus prone to metastasize. Limited follow-up on two patients indicated no recurrence of hormonal activity 9 months or more after excision (Contreras et al.; Wilkins and Ravitch).

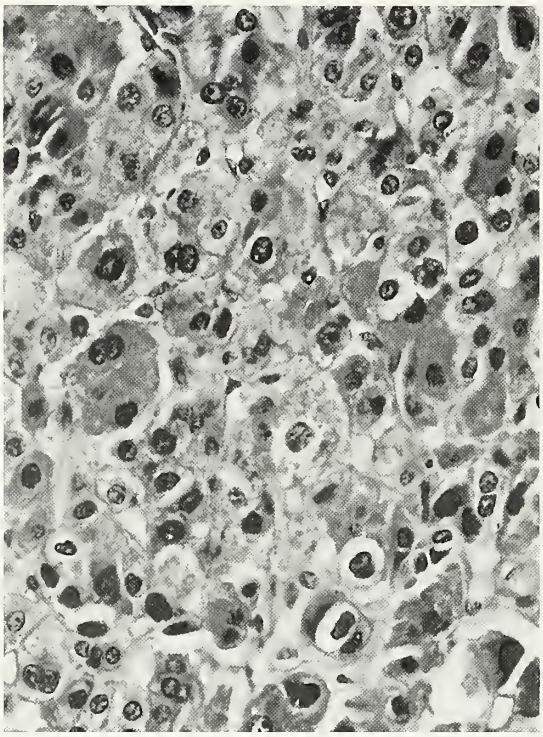


Figure 132
ADRENAL REST TUMOR

Adrenal rest tumor cells have moderate variation in size and shape, dense chromatin, and lack nucleoli. In this field, the cytoplasm is relatively eosinophilic and finely granular. X1240. (Courtesy of Dr. Albert Stanek, Brooklyn, New York.)

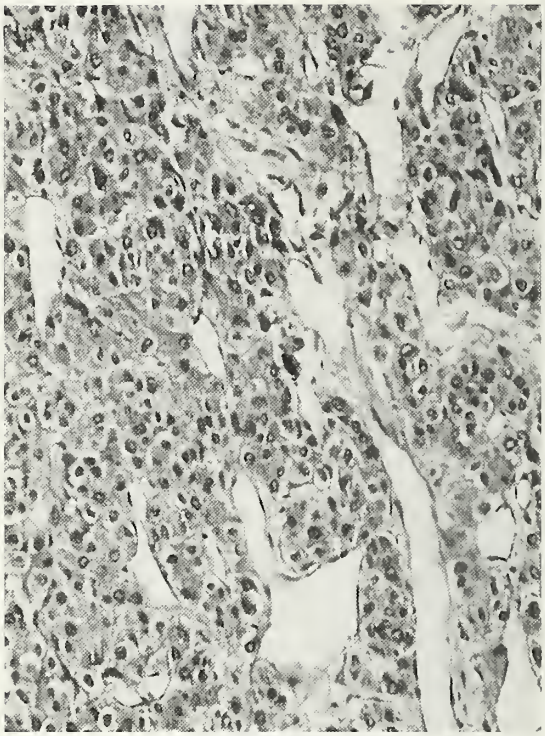
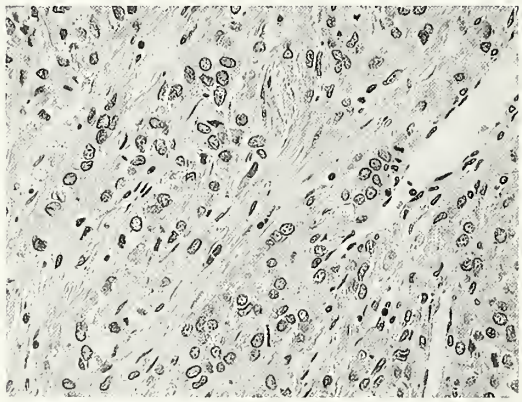


Figure 133
ADRENAL REST TUMOR

Trabecular growth pattern is formed in this area of the adrenal rest tumor. The vascular channels have an endothelial lining. X620. (Courtesy of Dr. Albert Stanek, Brooklyn, New York.)

A



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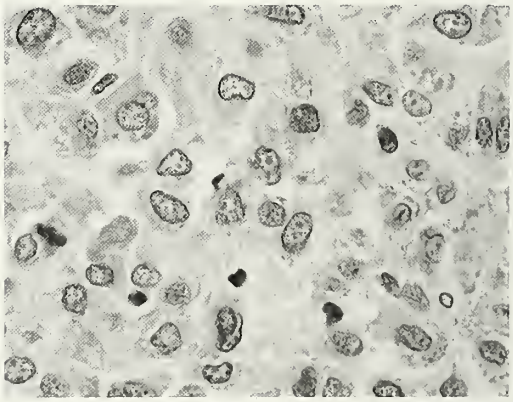


Figure 134
ADRENAL REST TUMOR

A. Trabecular growth separated by fibrous strands is noted in part of the adrenal rest tumor. X235. B. In this area of the tumor, moderately large polygonal cells with granular eosinophilic cytoplasm and lack of nucleoli are shown. X500. (Courtesy of Dr. Albert Stanek, Brooklyn, New York.)

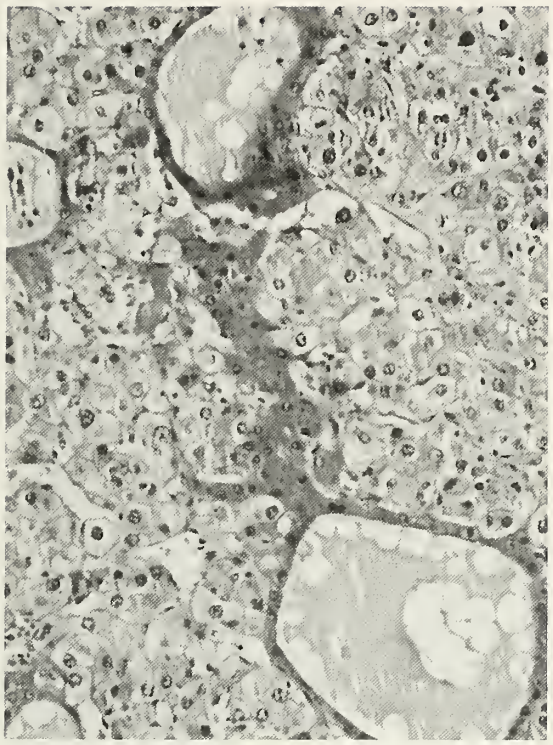


Figure 135
ADRENAL REST TUMOR
The acini seen in this figure are dilated hepatocellular glands. The hepatocellular pink cytoplasm contrasts with the pale clear cytoplasm of the tumor. X620.

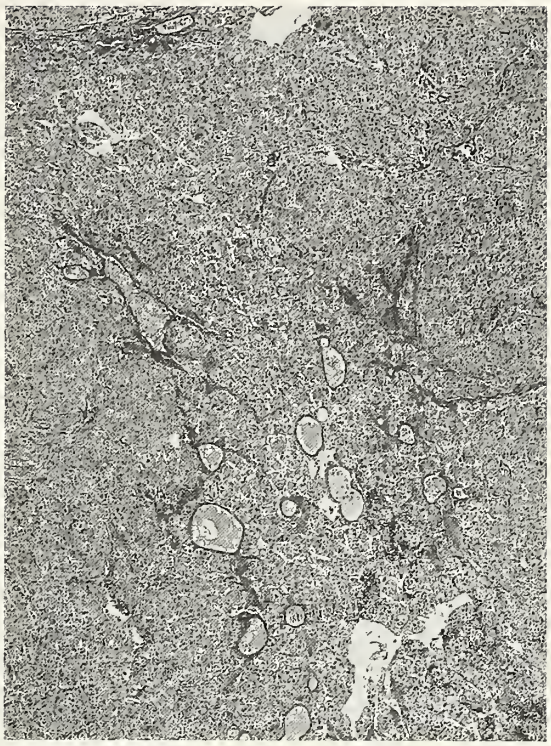


Figure 136
ADRENAL REST TUMOR
Sheets of polygonal cells with a few vascular spaces and dilated glands, which are acini formed by hepatocytes, characterize this functioning adrenal rest tumor. A rim of normal adrenal cortex was at one margin of the tumor, completely beneath Glisson's capsule. X125. (Courtesy of Dr. P. Contreras, Argentina.)

PRIMARY HEPATIC PHEOCHROMOCYTOMA

Definition. Pheochromocytoma is a tumor derived from adrenal medullary cells or paraganglion tissue that often has various atypical locations in the chest and abdomen. A primary hepatic pheochromocytoma must have catecholamine secretion or content demonstrated and also be the sole pheochromocytoma in the body, thereby excluding metastatic spread to the liver. The histologic features are similar to pheochromocytoma arising in the adrenal medulla, thus the tumor is composed of polygonal eosinophilic cells.

Incidence. Primary hepatic pheochromocytoma is unreported, but one patient came to our attention through the courtesy of Dr. Scott Saul at the University of Pennsylvania.

Clinical. A 16 year old male experienced sweating and a CT scan of the liver revealed a mass. Endocrine studies showed the hepatic venous drainage to contain the highest catecholamine levels,

and adrenal venous drainage was normal. The tumor was resected with the right lobe.

Pathology. The resected liver contained a solitary, well-circumscribed tumor of pale and focally dark brown tissue 4.8x4.3x3.3 cm near the capsule (pl. V-A). Fresh tissue was markedly fluorescent. Microscopic examination revealed a thick fibrous capsule and moderate variation in histologic appearance. Some areas have marked pleomorphism and variation in cell size and nuclear shape (fig. 137). Other areas have polygonal eosinophilic cells with small nuclei lacking nucleoli growing in a trabecular pattern, suggestive of fibrolamellar hepatocellular carcinoma (figs. 138, 139). Mitoses were not evident. Fibrous strands separate the cords of eosinophilic cells. Immunoperoxidase staining in extrahepatic, normally located pheochromocytoma reveals mixed results. Many tumors have a positive reaction for S-100 and neuron specific enolase, but results depend upon technic and are not diagnostic of pheochromocytoma.

Differential Diagnosis. A major consideration in primary hepatic pheochromocytoma is metastatic pheochromocytoma, but the venous catecholamine studies and CT scans indicated that no other pheochromocytoma was present in the referral patient (Saul). Metastatic pheochromocytoma occurs in 10 to 15 percent of pheochromocytomas, with the liver being second to the skeleton as the most common site for spread (Drasin). Fibrolamellar hepatocellular carcinoma has a similar histologic appearance to primary hepatic pheochromocytoma, having polygonal cells and thin lamellar fibrosis, but fibrolamellar hepatocellular carcinoma also has numerous other features including: prominent nucleoli; pale bodies; bile production; and prominent sinusoidal lining cells. In addition, no catecholamine output has been documented.

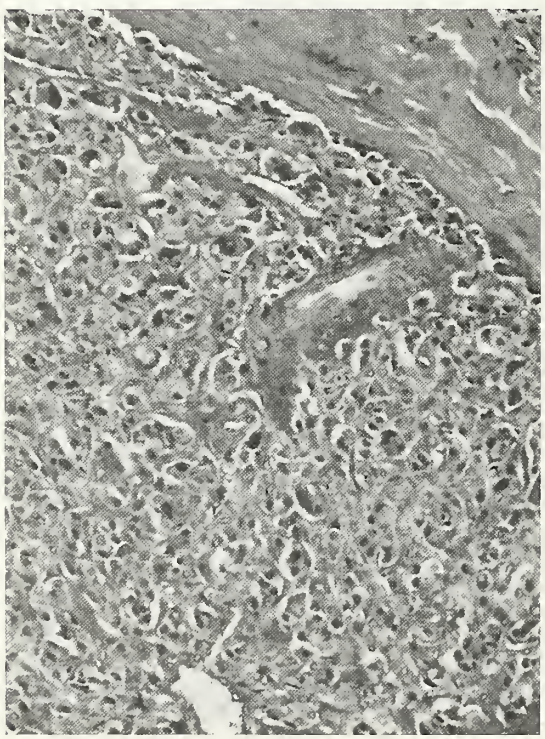


Figure 137
PRIMARY HEPATIC PHEOCHROMOCYTOMA
This hepatic pheochromocytoma has a fibrous capsule containing moderately pleomorphic, eosinophilic cells with marked variation in size and nuclear chromatin. X620. (Courtesy of Dr. Scott Saul, Philadelphia, Pennsylvania.)

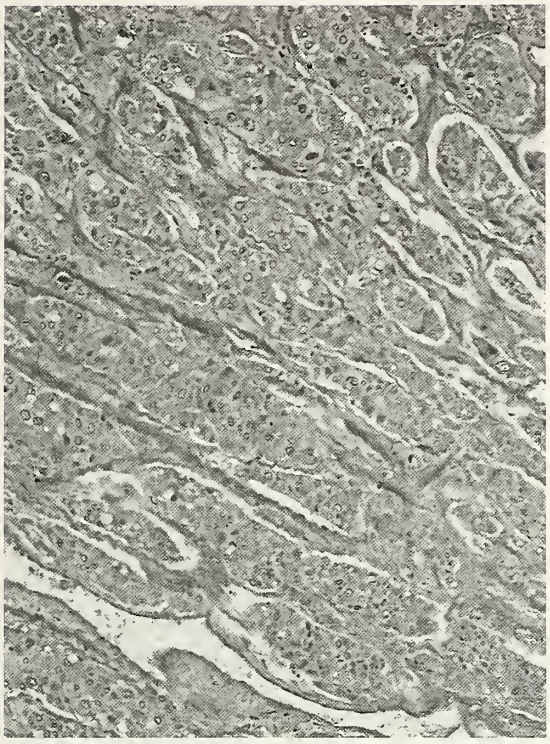


Figure 138
PRIMARY HEPATIC PHEOCHROMOCYTOMA
Trabecular growth with thin fibrous strands and widened vascular channels is common in this hepatic pheochromocytoma. X310. (Courtesy of Dr. Scott Saul, Philadelphia, Pennsylvania.)

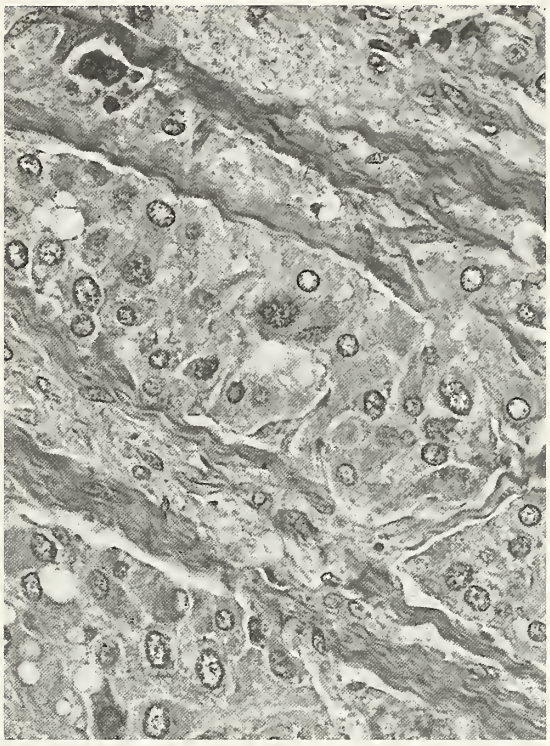


Figure 139
PRIMARY HEPATIC PHEOCHROMOCYTOMA
These moderately large, eosinophilic polygonal cells with round nuclei lacking nucleoli are similar to hepatocellular carcinoma. X1240. (Courtesy of Dr. Scott Saul, Philadelphia, Pennsylvania.)

PANCREATIC REST TUMORS

SYNONYMS AND RELATED TERMS: Intrahepatic pancreatic heterotopia; aberrant pancreatic insular carcinoma.

Definition. Intrahepatic pancreatic rest tumors are derived from heterotopic or ectopic pancreatic tissue located within the liver. Proof of origin from ectopic pancreatic tissue requires the presence of benign pancreatic acinar tissue, which may also contain islets of Langerhans and remnants of ductular elements, or the presence of islets of Langerhans remnants within a tumor similar to islet cell tumor originating in the pancreas.

Incidence. Heterotopic pancreatic tissue has been reported to occur in 0.6 to 5.6 percent of routine necropsies (Barbosa et al.). According to surgical material from 1946, it occurred in 1 in 500 operations in the upper abdominal region. Nickels and Laasonen reported a frequency of 1 in 380 surgical specimens in 1970. However, the most common locations for heterotopic pancreatic tissue are the duodenum, stomach, and jejunum, with one reported intrahepatic case in a survey of 471 patients with heterotopic pancreatic tissue.

Clinical. The majority of the usual heterotopic pancreatic rest tumors are found in males and discovered in adulthood (Ballinger; Mobini et al.). One patient experienced abdominal discomfort due to a large intrahepatic cyst. Another patient experienced hypoglycemia (Ballinger).

Gross. Mobini and associates reported a patient with a large, 7 cm in diameter (109 g) mass attached to the left lobe of liver by a small pedicle. Ballinger reported two large, gritty, fibrous masses (11x17 cm).

Microscopic. The cystic lesion had pancreatic exocrine tissue within the fibrous wall, as well as atrophic pancreatic ducts and acini. The cyst lining consisted of tall columnar cells and hepatic parenchyma was adjacent to the major part of the cyst wall. Ballinger's case showed sheets and small nests of cells arranged in a trabecular network. The cells were described as similar to the islets of Langerhans.

Differential Diagnosis. The identification of normal pancreatic tissue in heterotopic location and adjacent to the tumor indicates derivation of the tumor from the heterotopia. However, Ballinger's case did not have nontumor heterotopic tissue, and thus represents the more difficult problem of excluding metastatic islet cell carcinoma. Ballinger did demonstrate hormonal activity and the absence of a primary pancreatic lesion.

CARCINOID TUMOR

SYNONYMS AND RELATED TERMS: Peripheral neuroendocrine tumor of the liver; argentaffinoma; APUDoma of liver.

Definition. Primary hepatic carcinoid tumor has histologic features of the classic carcinoid (i.e., trabecular and pseudoglandular pattern) and dense core granules demonstrated by electron microscopy or by immunohistochemistry (i.e., positive staining by chromogranin antibody). Thorough clinical evaluation must exclude metastatic carcinoid tumor to the liver. Carcinoid tumors often have positive staining by Grimelius technic and positive immunoperoxidase reactions for chromogranin. Several hepatic tumors, including hepatocellular carcinoma and cholangiocarcinoma, have some of these features (i.e., chromogranin positive or neurosecretory granules), but not the appropriate light microscopic pattern of trabecular or pseudoglandular growth. Thus, we consider the latter group to be a special variant of the tumor recognized by light microscopy (i.e., hepatocellular carcinoma or cholangiocarcinoma).

Incidence. Primary hepatic carcinoid tumors are rare and are the subject of case reports. We have seen five carcinoid-like tumors, but do not have complete evaluation by immunoperoxidase or electron microscopy. Therefore, our cases do not meet the rigid criteria required to prove primary hepatic carcinoid. A 1974 review by the National Cancer Institute of 2837 carcinoid tumors revealed one from the gallbladder, but none were primary in the liver (Godwin).

Clinical. A few patients with large hepatic tumors have the carcinoid syndrome, but published reports indicate that these are usually hepatocellular carcinoma with endocrine features (see Variants). Warner and associates reported a 62 year old man with no clinical symptoms who had a large tumor that stained positive

for pancreatic polypeptide. Ali and colleagues reported a 48 year old woman with marked hypoglycemia, a large hepatic mass that had dense core granules by electron microscopy, and carcinoid-like histologic features. Our patients had no dominant clinical symptoms nor any urinary studies.

Pathogenesis. The rarity of the hepatic carcinoid tumor affords limited knowledge of its origin. Whereas carcinoid tumor arises in the gallbladder and oat cell carcinoma, a related tumor, arises in the biliary tree, it is likely that similar precursor cells for these tumors migrate within intrahepatic bile duct structures and form a nidus for neuroendocrine tumor production. Furthermore, because pancreatic rest tissue occurs in the liver and may contain islets of Langerhans, the hepatic carcinoid tumor may evolve by tumor development in such ectopic islet cell tissue. Alternatively, differentiation from biliary epithelium to carcinoid tumor may occur. Alpert and associates reported two cholangiocarcinomas with carcinoid features. Therefore, the composite glandular-endocrine carcinomas noted in the gastrointestinal tract may have a similar counterpart in the liver (Lewin).

Gross. Hepatic carcinoid tumors are well-circumscribed, nonencapsulated, large, bulky, hemorrhagic tumors with gray-white areas. Due to the abundant blood supply, two of our tumors resembled angiosarcoma. Hepatic carcinoid tumors occur in the noncirrhotic liver and the tumor often has marked calcification. We are unaware of any gross differences in the functioning tumors compared to the nonfunctioning tumors.

Microscopic. Carcinoid tumors have a pseudoglandular pattern or a mixture of trabecular and pseudoglandular patterns (figs. 140-143). The tumor cells are small, uniform, polygonal cells with moderately abundant, eosinophilic, granular cytoplasm and round nuclei with small or absent nucleoli. Fibrosis may be scanty or abundant and surround nests of cells (figs. 142, 143). Electron microscopy reveals uniform, dense core granules, typically 200 nm in diameter (fig. 144) (Phillips et al.).

Differential Diagnosis. Metastatic carcinoid tumor is the major concern and a search for a primary within the small intestine, stomach, and pancreas is essential for diagnosis of primary hepatic carcinoid tumor. A large single mass is typical for primary hepatic pheochromocytoma, whereas multiple diffuse nodules are characteristic of metastatic carcinoid tumor. Hepatocellular carcinoma may have a similar histologic appearance at low magnification, but hepatocellular carcinoma has prominent nucleoli, usually has acinar structures with bile formation, arises in a cirrhotic liver, and has prominent sinusoidal lining cells around the trabeculae. Cholangiocarcinoma may be confused with hepatic carcinoid tumor because of the similar small cells and fibrosis, but the presence of dense core granules or chromogranin positivity is a feature of carcinoid. Some cholangiocarcinomas may have areas of carcinoid tumor (Alpert et al.).

Variants. Hepatocellular carcinoma has been reported with carcinoid features, including explosive diarrhea, increased urinary excretion of 5-hydroxyindoleacetic acid, and dense core granules by electron microscopy (Primack et al.). Barsky reported a 43 year old man with hepatic tumor that had dense core granules and

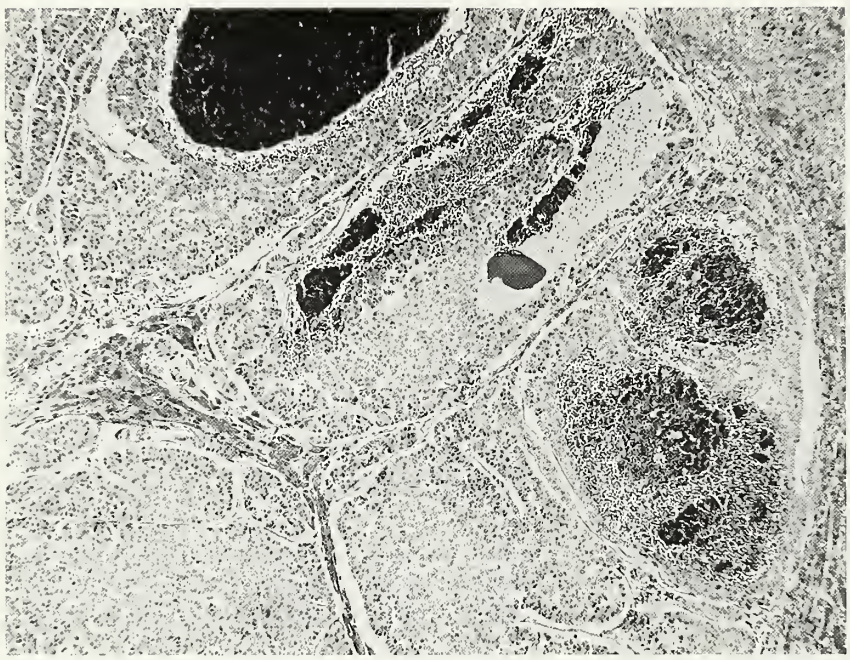


Figure 140
(Figures 140 and 141 are from the same patient)
CARCINOID TUMOR
This hepatic carcinoid tumor has prominent vascularity within large masses of uniform small cells that compress the adjacent liver by bulging growth. X70.

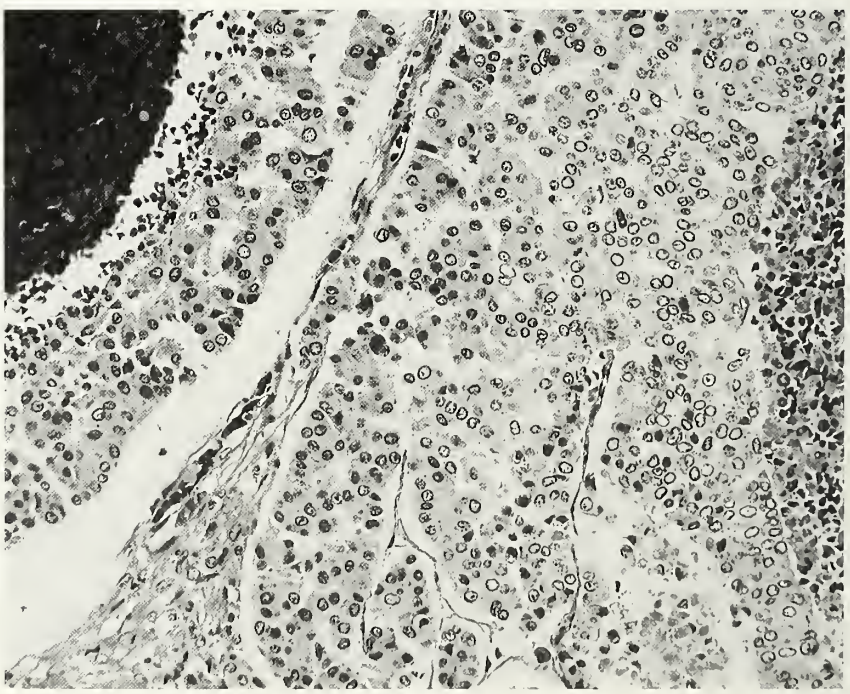


Figure 141
CARCINOID TUMOR
Small uniform cells without nucleoli form trabeculae and no sinusoidal lining are noted in the large blood-filled space. X250.

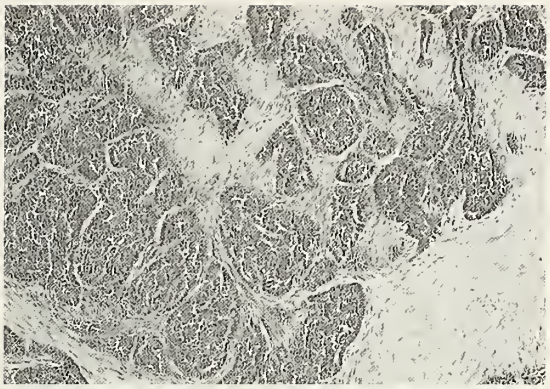


Figure 142
(Figures 142-144 are from the same patient)
CARCINOID TUMOR

This primary hepatic carcinoid tumor was diagnosed in an adult who had hepatomegaly for years and an extensive tumor only in the liver. The biopsy showed fibrosis surrounding nests of uniform small cells. X210. (Courtesy of Dr. M.J. Phillips, Toronto, Canada.)

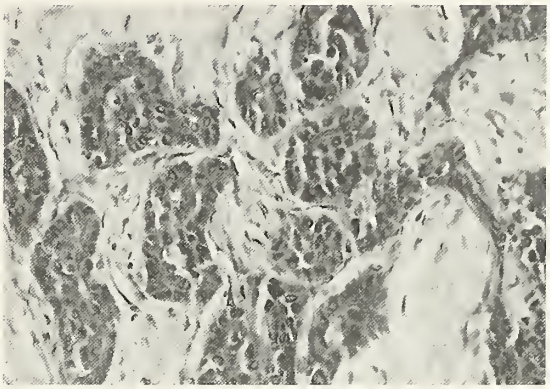


Figure 143
CARCINOID TUMOR

Small cuboidal cells with eosinophilic cytoplasm and round small nuclei are seen in this figure. X840. (Courtesy of Dr. M.J. Phillips, Toronto, Canada.)

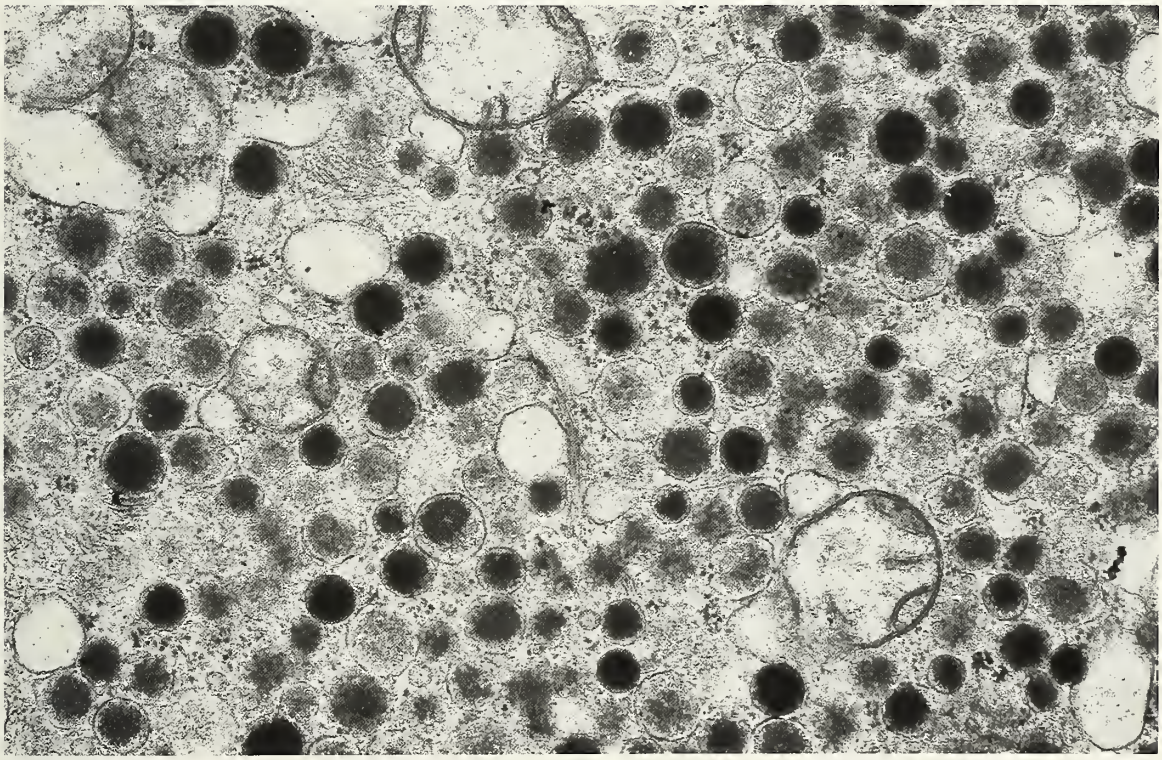


Figure 144
CARCINOID TUMOR

An electron micrograph of the hepatic carcinoid tumor in figure 143 shows numerous uniform, dense core granules. X38,000. (Fig. T52A from Phillips, M.J., Poucell, S., Patterson, J., et al. The Liver. An Atlas and Text of Ultrastructural Pathology, p. 545. New York: Raven Press, 1987.)

immunochemical staining for a neuroendocrine peptide, as well as histologic features of both hepatocellular carcinoma and carcinoid. Therefore, clinical symptoms may promote a search for endocrine function of a hepatic tumor, but the report by Norgaard and Bardram indicates that these symptoms may not be required to justify this search. In their patient, a resected hepatic tumor had histologic features of hepatocellular carcinoma, including large nucleoli, PAS positive granules, trabecular growth, and dense core granules typical of neuroendocrine origin.

NEUROENDOCRINE INFANTILE SINUSOIDAL TUMOR

Platt and associates reported two infants (ages 5 weeks and 6 months) with an apparently primary hepatic tumor. At surgery, the liver was uniformly enlarged without definite nodularity. Liver biopsies revealed sinusoidal infiltration by small, round to oval cells (fig. 145) and neurosecretory granules were identified by electron microscopy. Chemotherapy was administered and the children remained free of disease more than 8 years later. Metastatic neuroblastoma was considered a more likely diagnosis, but a careful search failed to support that diagnosis.

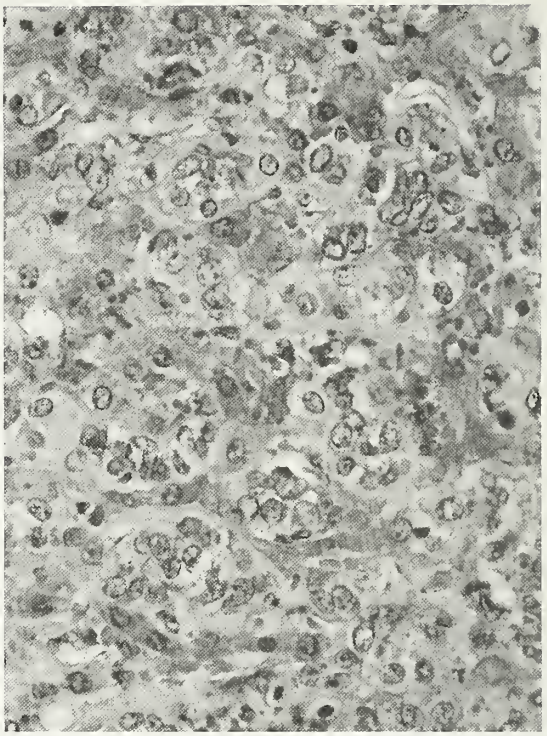


Figure 145
NEUROENDOCRINE INFANTILE SINUSOIDAL TUMOR
In this figure, cords of atrophic hepatocytes with eosinophilic cytoplasm are surrounded by sinusoidal infiltration of small to moderate round cells with indistinct cytoplasm. Mitoses are not common. X1240. (Courtesy of Dr. M.S. Platt, Akron, Ohio.)

TERATOMA

SYNONYMS AND RELATED TERMS: Teratoblastoma; teratoid tumor; tridermoma.

Definition. Hepatic teratoma is composed of benign tissue derived from all three germ layers and elements foreign to the adult liver. The presence of malignant teratomatous components, such as yolk sac carcinoma, are not reported in hepatic teratomas, and if present, the tumor should be classified by that component (See Yolk Sac Tumor).

Incidence. Hepatic teratomas are rare; prior to 1977, a total of 24 patients were reported (Todani et al.). Two additional patients have been reported since 1977 (Dische and Gardner; Watanabe et al.). The majority of the surveys of hepatic tumors from the Children's Hospital Los

Angeles revealed no teratomas (Landing) and surveys of teratomas in children revealed none in the liver (Berry et al.; Pear and Boline).

Clinical. Children comprised 17 of the 24 patients reviewed by Todani and associates. Hepatic teratoma is noted within the first year in most patients; 25 percent are recognized at birth (Dische and Gardner). Female predominance occurs and the primary clinical problem is abdominal mass. The tumors often have calcification and are large when identified. Four reported patients had the tumor in adult life and one had had the tumor since childhood.

Pathogenesis. The origin of these tumors remains unknown, although origin from an ectopic primordial germ cell has been proposed. A report of two teratomas (one hepatic and one in the neck), trisomy-13, and the frequent occurrence in the first year suggested congenital malformation as a likely origin (Dische and Gardner).

Gross. Hepatic teratoma is similar to teratoma arising in other locations and thus is a large, multicystic mass with a mixture of solid, hard, soft, and cystic tissue. Although cartilage and bone are noted, hepatic teratomas rarely have the tooth and hair structures typical of ovarian teratomas. However, Watanabe and colleagues reported a hepatic teratoma with tooth-like structures and hair.

Microscopic. A wide variety of embryonal tissue is recognized. Bone, cartilage, and primitive renal, pancreatic, and other endocrine tissue may be noted (figs. 146-149). Mature squamous epithelium and hair also may occur, as well as neural tissue (fig. 148). In one case, the hepatic teratoma contained hepatic tissue with extramedullary hematopoiesis (fig. 149) (Watanabe et al.). Malignant teratomatous tissue is apparently rare and includes squamous carcinoma and sarcomatous mesenchyme, yet overt yolk sac carcinoma components are not seen (Misugi and Reiner). Histologic features of adult hepatic teratomas are similar to those in children (Watanabe et al.).

Prognosis. Hepatic teratomas with benign elements occurring in early childhood have often been successfully resected (Dische and Gardner; Yarbrough and Evashwick), whereas the few adults have died, either from other disease or metastasis of the malignant component.

Differential Diagnosis. Distinction of hepatic teratoma from other hepatic tumors is usually not difficult. Yolk sac tumor is almost entirely composed of a highly malignant component and lacks any benign germ cell tumor component. Malignant hepatic mixed tumor has derivatives from two germ layers with malignant change in some mesenchymal elements; most often the epithelial component is not hepatocellular.

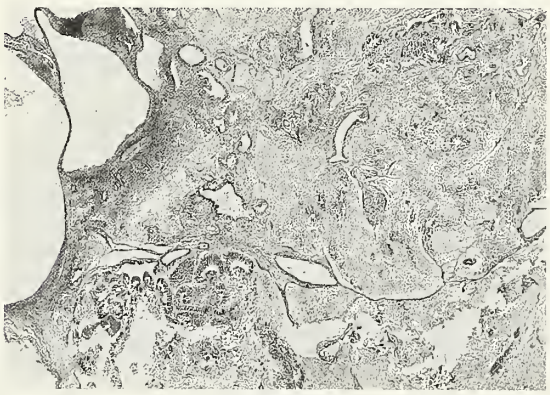


Figure 146
TERATOMA
This hepatic teratoma from a 22 week old stillborn fetus has multiple squamous-lined cysts and adjacent primitive neuroectodermal tissue. X40. (Courtesy of Dr. Wilmer Talbert, Long Beach, California.)

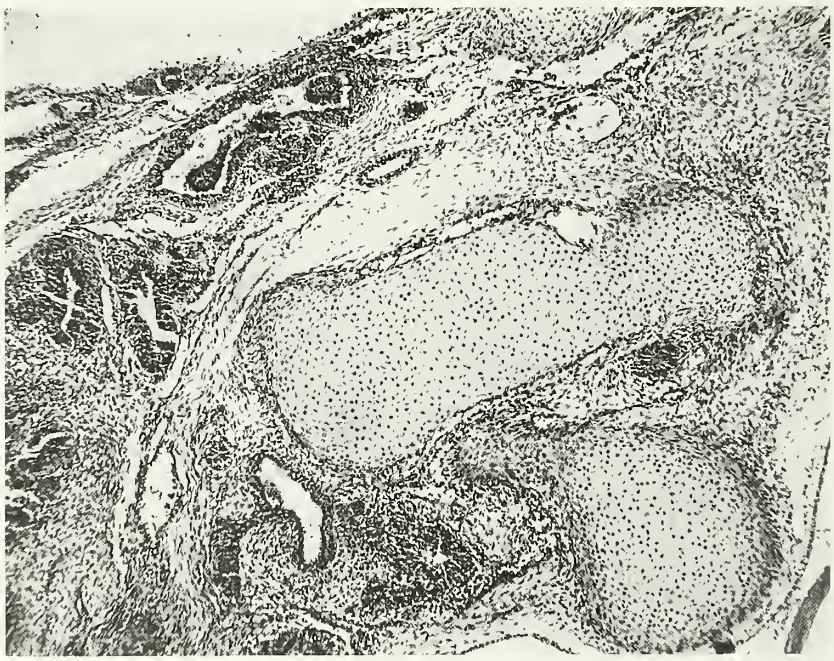


Figure 147
(Figures 147-149 are from the same patient)
TERATOMA
This hepatic teratoma has cartilage and numerous cysts lined by transitional and squamous epithelium. X40.

Figure 148
TERATOMA
An embryonic eye in a formative stage is seen in this teratoma. The outer layer has melanocytic pigment. X120.

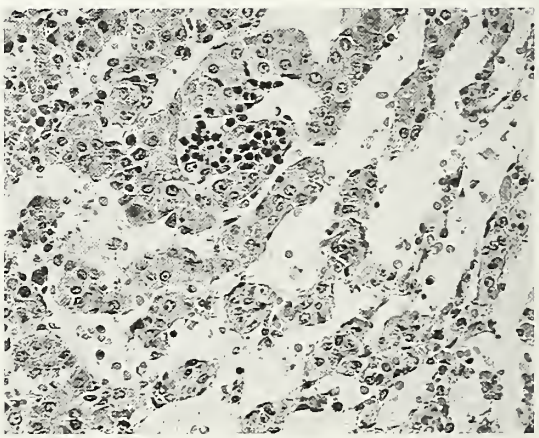


Figure 149
TERATOMA
This area of hepatic teratoma contains primitive hepatocytes with extramedullary hematopoiesis. X120.

YOLK SAC TUMOR

SYNONYMS AND RELATED TERMS: Endodermal sinus tumor; mesonephroma; infantile embryonal carcinoma (of testis or ovary).

Definition. Yolk sac tumor is a rare tumor usually arising in the ovary or testis of young children. It occurs in extragonadal sites and, rarely, in the liver. The tumor has distinctive but variable histologic features.

Incidence. A total of five patients are known to us: one with hepatic yolk sac tumor that has been well-described; two with tumors in the ligamentum teres (Weinberg and Finegold); and two that were referred to us.

Clinical. Two of our three patients were young males (18 and 30 months); the third patient was a 35 year old woman with an intrahepatic mass and omental metastasis, but no tumor in the resected ovaries. The youngest patient had abdominal distention, fever, and a large palpable abdominal mass. The large hepatic mass was resected and he died of disseminated disease 7 months later. No gonadal masses were detected by careful examination. Hepatic enlargement had been suspected in the second child for many months, and a large hepatic mass, 12 cm in diameter, was resected from the right lobe with part of the right diaphragm, rib cage, and abdominal wall. No scrotal mass was detected and he died 18 months later. Laboratory studies in these two patients included anemia and elevated serum α-fetoprotein, which was a helpful marker of tumor recurrence in one patient.

Pathogenesis. Yolk sac tumor, originally thought to be derived from primitive mesonephros and a variant of choriocarcinoma, is now believed to be derived from the yolk sac (Huntington and Bullock; Teilum). The histochemical and histologic similarities of the developing rat placenta led Teilum to conclude that the endodermal sinus tumor was derived from the yolk sac. The development of extragonadal germ cell tumor is attributed to the migration of germ cell elements to unusual sites (Pierce and Abell). Curiously, teratoma of the liver does not include any yolk sac tumor components.

Pathology. These tumors are circumscribed, encapsulated, large masses arising in the normal liver (fig. 150). The cut surface is variegated with pale yellow, and

Figure 150
(Figures 150, 151, and Plate V-B are from the same patient)
YOLK SAC TUMOR
This figure shows a multinodular surface of the yolk sac tumor (12.5x9x7 cm) resected from a 30 month old male. (Courtesy of Dr. Frank J. Glassy, Sacramento, California.)

granular areas are mixed with translucent mucoid gray areas, as well as hemorrhagic, necrotic areas (pl. V-B). The variable histologic pattern matches the variation in texture seen by gross examination and numerous sections may be needed to identify the diagnostic features. There may be large areas of necrosis, myxoid stroma with vascular spaces lined by thin endothelial cells, and transition to broad sheets of polygonal basophilic cells (figs. 151-153). A variety of vascular spaces are noted, some containing papillary projections that resemble glomerular bodies with a lining of hobnail-shaped cells (Schiller-Duval bodies) (fig 153). Within the myxoid areas, the polygonal cells often have hyaline globules and transition to clear cell areas. These hyaline globules are α-fetoprotein, albumin, α-1-antitrypsin, and transferrin (Shirai et al.).

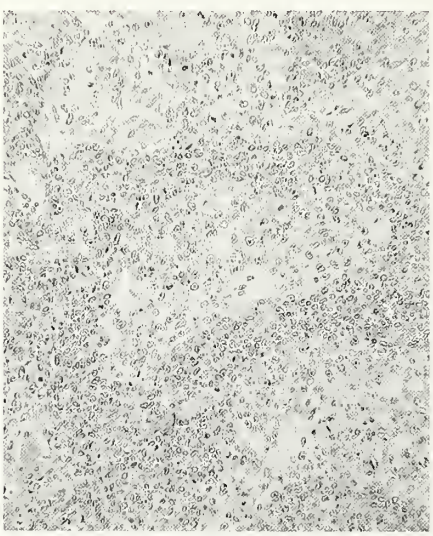


Figure 151
YOLK SAC TUMOR
Yolk sac tumor has a variegated pattern of basophilic polygonal small cells within an edematous stroma. X117. (Courtesy of Dr. Frank J. Glassy, Sacramento, California.)

Differential Diagnosis. The first diagnostic consideration is metastatic yolk sac tumor from the ovary or testis, or even from other nonhepatic extragonadal yolk sac tumors. Metastasis from other germ cell tumors, including teratocarcinoma or germinoma, may mimic yolk sac tumor; search for the Schiller-Duval bodies, as well as the hyaline globules and pattern of intercommunicating channels, assists in recognizing yolk sac tumor.

Prognosis. Two young males with hepatic resection of yolk sac tumors were given triple chemotherapy and died with metastatic tumors 7 and 18 months after diagnosis.

MALIGNANT HEPATIC TROPHOBLASTIC TUMOR

SYNONYMS AND RELATED TERMS: Placental site trophoblastic tumor.

Definition. Malignant hepatic trophoblastic tumor is a tumor that occurs in women of reproductive age. Multiple masses of eosinophilic and polygonal cells resembling cytotrophoblasts produce severe intrahepatic hemorrhage.

Incidence. A single report describes two patients (Heaton et al.).

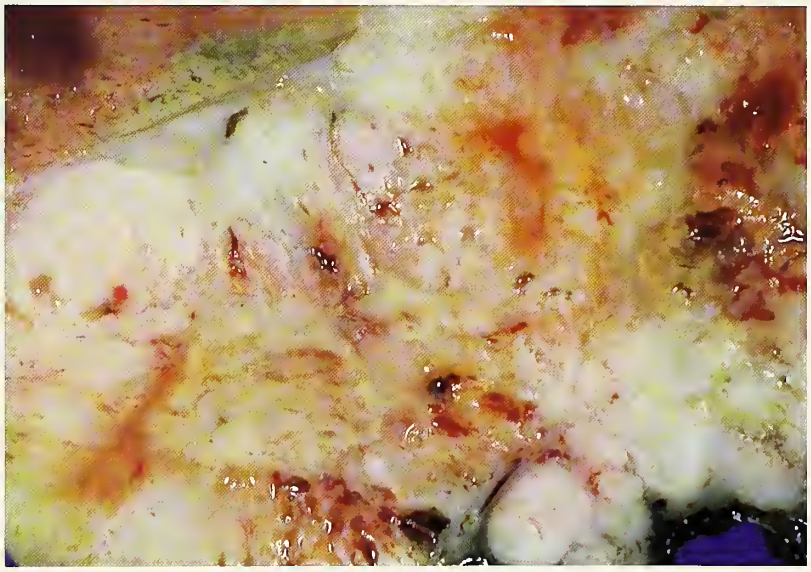
Clinical. Two women, ages 27 and 29 years, on oral contraceptives for 7 to 8 years, had hepatic mass and abdominal pain. In one patient, massive intraperitoneal hemorrhage occurred and multiple bleeding tumor nodules were noted in the left lobe of the liver. The other patient had a 5 cm, multinodular, hemorrhagic tumor in the right lobe, which was resected. The serum β-HCG levels were 3000 and 4800 IU/ml in each patient. The endometrium had no evidence of choriocarcinoma.

PLATE V

A. PRIMARY HEPATIC PHEOCHROMOCYTOMA

(Plate V-A and figures 137-139 are from the same patient)

This 700 g resected right lobe of the liver from a 16 year old male with primary hepatic pheochromocytoma contains a 4.8 x 4.3 x 3.3 cm mass near the superior surface and adjacent to the capsule. (Courtesy of Dr. Scott Saul, Philadelphia, Pennsylvania.)



B. YOLK SAC TUMOR

(Plate V-B and figures 150, 151 are from the same patient)

The cut surface of this yolk sac tumor is a mixture of cream-gray and gray-purple bosselated tissue with a 1 mm capsule. (Courtesy of Dr. Frank J. Glassy, Sacramento, California.)

Figure 152
(Figures 152 and 153 are from the same patient)
YOLK SAC TUMOR
Variegated pattern of edematous stroma with numerous channels and areas of polygonal small proliferation are typical of this yolk sac tumor. X310. (Courtesy of Dr. Jeannie McMahon, Los Angeles, California.)

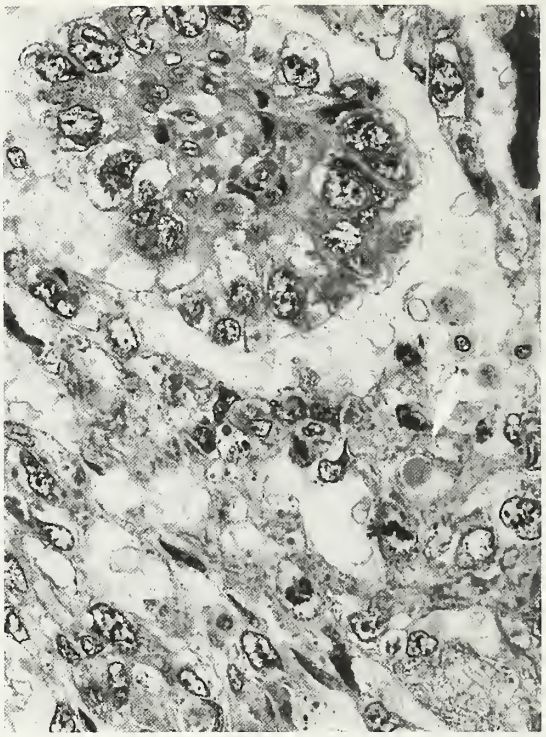


Figure 153
YOLK SAC TUMOR
A Schiller-Duval body resembles a glomerulus with papillary structure. The arrow points to a small, intracytoplasmic, hyaline globule in a yolk sac tumor. X1240. (Courtesy of Dr. Jeannie McMahon, Los Angeles, California.)

Pathogenesis. This unusual tumor may derive from an ectopic germ cell similar to other extragenital choriocarcinoma. There is no evidence within the two known malignant hepatic trophoblastic tumors of germ cell origin. Metastatic choriocarcinoma must be excluded by thorough clinical evaluation. Secondly, because elevated serum β-HCG occurs in hepatoblastoma and hepatocellular carcinoma (Nakanuma et al.), malignant hepatic trophoblastic tumor may be derived by metaplasia of hepatic epithelium. The course of one patient with malignant hepatic trophoblastic tumor after chemotherapy and the lack of any hepatocellular carcinoma-like areas in the other patient indicates that origin from hepatocellular carcinoma is unlikely.

Pathology. A large hemorrhagic tumor replaced half of the liver of one patient. Moderately large eosinophilic cells with a moderate degree of nuclear variation and few nucleoli (figs. 154-156), as well as multinucleated large cells, were present. A dimorphic pattern of choriocarcinoma was lacking and the polygonal cells resembled

Figure 154
(Figures 154 and 155 are from the same patient)
MALIGNANT HEPATIC TROPHOBLASTIC TUMOR
This malignant hepatic trophoblastic tumor has a sharp margin and a thin fibrous capsule separating the normal liver from the papillary eosinophilic tumor. X60. (Courtesy of Dr. William Christopherson, Louisville, Kentucky.)

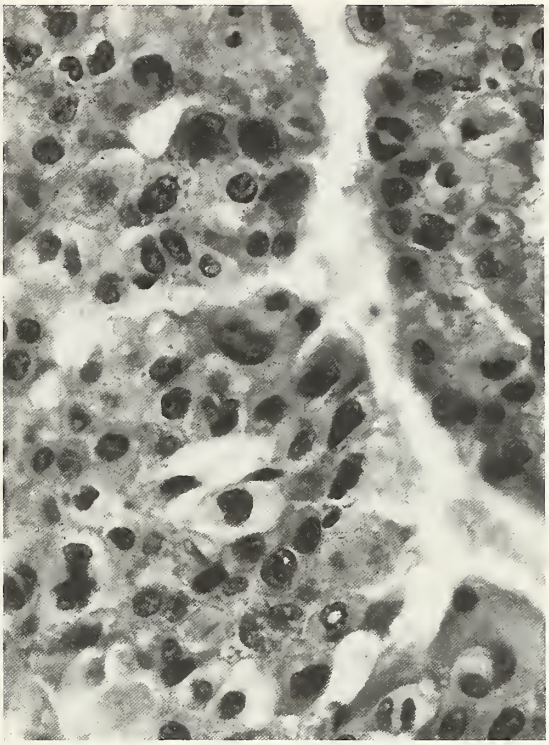


Figure 155
MALIGNANT HEPATIC TROPHOBLASTIC TUMOR
This higher magnification of the malignant hepatic trophoblastic tumor shows regular eosinophilic cells with mild variation in nuclei that lack nucleoli and form clusters without sinusoidal lining cells. X1240. (Courtesy of Dr. William Christopherson, Louisville, Kentucky.)

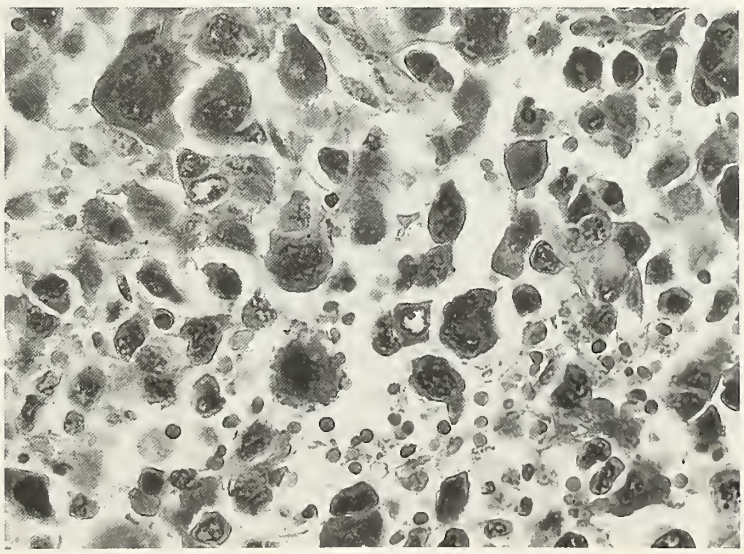


Figure 156
MALIGNANT HEPATIC
TROPHOBLASTIC TUMOR
Another area of the malignant hepatic trophoblastic tumor has marked pleomorphism with marked variation in cell size and multinucleated cells. X1240. (Courtesy of Dr. William Christopherson, Louisville, Kentucky.)

intermediate trophoblastic cells with an absence of syncytiotrophoblasts. The malignant hepatic trophoblastic tumor resembles placental site trophoblastic tumor (Young and Scully). Immunohistochemical stains are positive for both HCG and human placental lactogen.

Differential Diagnosis. The most common explanation for such histologic findings is metastatic choriocarcinoma or metastatic anaplastic carcinoma. Careful search of the uterus and ovaries for a primary lesion is essential. Immunochemical staining and the serum studies help clarify the histologic findings as trophoblastic in origin.

Prognosis. One patient died of peritoneal hemorrhage and the other patient is free of tumor nearly 2 years after the diagnosis and chemotherapy for presumptive diagnosis of metastatic choriocarcinoma.

HEPATIC MALIGNANT MIXED TUMOR

SYNONYMS AND RELATED TERMS: Hepatic mixed tumor; malignant teratoma; malignant nonhepatocytic mixed tumor.

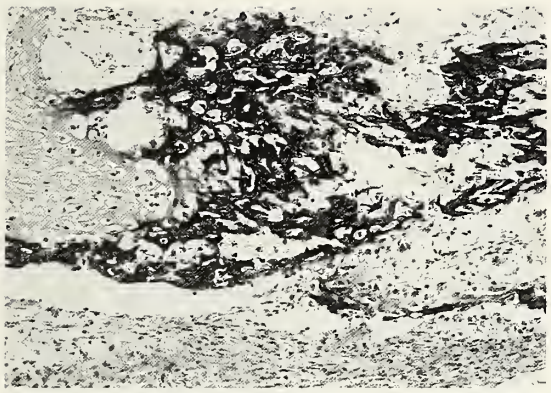
Definition. Hepatic malignant mixed tumor is composed of malignant mesenchymal elements and benign or malignant epithelial elements. The mesenchymal derivatives include bone and cartilage, but ectodermal derivatives are lacking; thus, hepatic malignant mixed tumor does not meet the criteria of malignant teratoma. Hepatic malignant mixed tumors are usually rapidly fatal.

Incidence. Kawarda and associates identified 22 cases in the literature and added two of their own. Some of the reported cases are now known to be epithelioid hemangioendothelioma. We have four hepatic malignant mixed tumors in our consultation files.

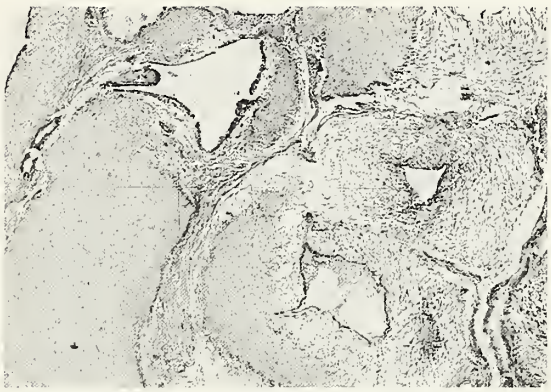
Clinical. The average age of patients with hepatic malignant mixed tumor is 52 years with a male predominance. Abdominal mass and pain develop quickly and surgery was performed in one patient. Hepatic resection of a pedunculated, large, 4000 g left lobe hepatic malignant mixed tumor was reported (Kawarda et al.).

Pathology. Hepatic malignant mixed tumors are large and bulky with a mixture of gray-red, hard nodules containing hemorrhage and soft fibrous tissue. The liver may be extensively replaced. Microscopic features show a variety of histologic patterns including chondrosarcoma, rhabdomyosarcoma, fibrosarcoma, and adenocarcinoma (figs. 157-159). Hepatocellular differentiation is not noted and numerous sections are advised to classify all the histologic components.

Differential Diagnosis. Exclusion of tumors with hepatocellular differentiation is desirable, as many previously reported examples of hepatic mixed tumors are primarily hepatocellular carcinoma with focal sarcomatous metaplasia. Such hepatocellular tumors have a different histologic appearance than mixed tumors with abundant mesenchymal sarcoma and nonhepatocytic epithelial components. Metastatic germ cell tumors are a primary concern that requires careful search of the extrahepatic tissue.



A



B

Figure 157
(Figures 157-159 are from the same patient)
HEPATIC MALIGNANT MIXED TUMOR

A. Calcified osteoid and chondrosarcoma form large masses in this hepatic malignant mixed tumor. X210. B. Large areas of chondrosarcoma and edematous stroma surround thin layers of adenocarcinoma. X85. (Courtesy of Dr. Y. Kawarda, Mie, Japan.)

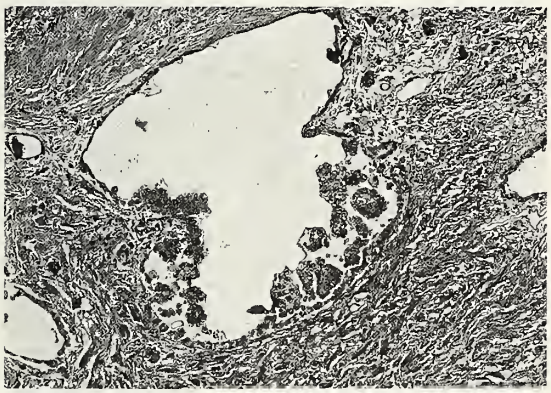


Figure 158
ADENOCARCINOMA

As noted in this figure, papillary adenocarcinoma forms small cysts in the hepatic malignant mixed tumor. X210. (Courtesy of Dr. Y. Kawarda, Mie, Japan.)

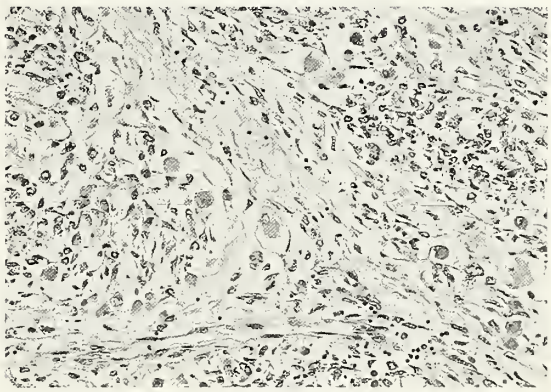


Figure 159
RHABDOMYOSARCOMA

This rhabdomyosarcoma has prominent eosinophilic rhabdomyoblasts. X420. (Courtesy of Dr. Y. Kawarda, Mie, Japan.)

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PRIMARY MALIGNANT EPITHELIAL TUMORS

Hepatocytes and bile duct epithelial cells give rise to the majority of hepatic carcinomas. The mucous glands of the common hepatic duct extend a variable distance along the wall of the major intrahepatic ducts and provide another cell of origin; ectopic tissue provides another source for epithelial tumors. Because both neoplastic and nonneoplastic hepatic cords appear to be converted to duct-like structures, routine histologic examination does not always allow classification by the cell of origin (hepatic versus bile duct). In our series of hepatocellular carcinomas, 15 percent have minimal duct-like or glandular areas and 5 percent have substantial ductal growth pattern. Such areas have promoted the concept of mixed ductal hepatocellular carcinoma (Goodman et al.). However, we have classified most such tumors as hepatocellular carcinomas. Furthermore, even tumors that are predominantly ductal occasionally have some cells that resemble hepatocytes and bile secretion may be present. Thus, a clear distinction is not always possible. Special technics such as immunohistochemistry and electron microscopy may assist in classification.

Adequate sampling is essential for accurate classification. In large tumors, the more tissue blocks examined, the more variation may be noted, both in histologic pattern and anaplasia. The giant cell carcinoma reported by Kuwano and associates illustrates such marked variation and the geographic diagram of one tumor depicts the variation in histologic appearance. In some instances, metastasis of hepatocellular carcinoma may appear as an unusual histologic pattern (such as spindle cell) and this metastatic lesion may be the first clinical sign of tumor. Because the histologic pattern in the metastatic lesion may be atypical, the liver may not be considered in the search for a primary site. A careful and thorough review of hepatic tumors has demonstrated wide variation in histologic patterns and these patterns may have special clinical importance helpful in the diagnosis of hepatocellular carcinoma.

HEPATOCELLULAR CARCINOMA

SYNONYMS AND RELATED TERMS: Hepatoma; malignant hepatoma; liver cell carcinoma; primary hepatocellular carcinoma; primary hepatic carcinoma. The term "hepatoma" does not denote the cell of origin and its use is discouraged.

Hepatocellular carcinoma is the most common primary epithelial neoplasm of the liver and its classification and recognition can be challenging. Adequate sampling of the tumor is essential for proper diagnosis and classification. Typical growth patterns (both gross and microscopic) are useful in the recognition of hepatocellular carcinoma, but the variation of patterns within the same tumor complicates the exact classification within a subtype. In general, if the majority of the tumor is a specific subtype (i.e., fibrolamellar, spindle cell or giant cell), then we prefer that subtype for classification. We recognize that a major clinical manifestation (such as metastasis) may be a first presenting sign, yet the bulk of the hepatocellular carcinoma utilized for classification may be a typical trabecular

hepatocellular carcinoma. "Combined" hepatocellular carcinoma usually applies to the specific combination of hepatocellular carcinoma (any subtype included) and cholangiocarcinoma. The term "mixed" is reserved for the combination of malignant mesenchymal and epithelial tumor, as in hepatic malignant mixed tumor.

Definition. Hepatocellular carcinoma is a malignant tumor derived from the hepatocyte and usually occurs in association with chronic liver disease, such as cirrhosis. Several clinical and histologic patterns are recognized and the prognosis may differ according to associated conditions and extent of tumor at diagnosis.

Incidence. The incidence and etiologic factors of hepatocellular carcinoma varies dramatically around the world. Within the United States, the occurrence of hepatocellular carcinoma varies in different ethnic groups. According to the World Health Organization, it is as low as 0.9 per 100,000 in New York women, to as high as 39.9 per 100,000 in San Francisco men (immigrant and Chinese-American combined). In European countries, the incidence is similar to most of the United States, with a rate of 0.145 percent in England reported by Cruickshank (1947-1959) and 0.45 percent reported by MacSween (1900-1969), but in Japan the rate varies from 2.58 percent in 1969 to 4.8 percent in 1978 (Nakashima et al., 1983). An estimated 9000 patients developed hepatocellular carcinoma in 1980 in the United States (Chlebowski et al.).

An increasing incidence of hepatocellular carcinoma has been noted worldwide. At the turn of the century, reports of incidence were 0.05 percent and 0.13 percent (Eggel). In our material (Table 6), the change in hepatocellular carcinoma by year increased from 0.15 percent in the first group to 1.48 percent in the last group.

Clinical. The clinical features of hepatocellular carcinoma vary with the underlying associated conditions. In a large U.S. population, a mixture of clinical conditions occurs due to the variety of ethnic groups, diversity of metabolic disorders, difference in exposure to viral agents, alcoholism, and environmental conditions. A 6-year experience (1976-1982) by four major Los Angeles hospitals including the LACUSC Medical Center was reported by Chlebowski and associates. This group of 121 patients (from charity and university referral centers) was diverse in racial origin: 57 white; 26 Oriental; 25 black; and 15 Hispanic

Table 6

CHANGING OCCURRENCE OF HEPATOCELLULAR CARCINOMA AT LACUSC MEDICAL CENTER AND USC LIVER UNIT

	1918-1953	1954-1963	1964-1973	1974-1983
Autopsy number	49,915	23,476	15,380	6,427
Hepatocellular carcinoma number	75	79	135	95
Percentage	0.15%	0.34%	0.88%	1.48%

patients. This contrasts with the predominantly white population in the large series reported by Edmondson and Steiner in 1954. The average age in the L.A. County multihospital series was 52 years, similar to the 55.9 years in the large national Japanese series of 1047 patients (Liver Cancer Study Group of Japan, 1984). Males predominate in both series (74 and 77 percent); cirrhosis is common in both (63 percent in the United States and 78 percent in Japan) and increased to 83.2 percent of hepatocellular carcinomas in the sixth report of the Liver Cancer Study Group of Japan (1987). Presenting symptoms of hepatocellular carcinoma include abdominal pain, abdominal fullness, mass, anorexia, weight loss, jaundice, malaise, and fever.

Atypical clinical signs and symptoms occur in 25 percent of patients and a similar number have evidence of metastasis at the time of diagnosis. Paraneoplastic syndromes (endocrine and atypical biochemical features) are rare, but may be distinctive. In the L.A. series, hypoglycemia was noted in two patients and erythrocytosis in one patient.

Laboratory studies do not reveal a diagnostic pattern unless clinical and laboratory findings are correlated. Whereas the majority of hepatocellular carcinoma patients have some abnormal routine serum laboratory results, no diagnostic pattern is present. Serum α-fetoprotein, a serum protein detected normally in the fetus, synthesized by the embryonic liver and gastrointestinal mucosa but absent in adults, has been an important marker for detection of hepatocellular carcinoma as well as other nonhepatic conditions, including embryonic tumors (Wepsic and Kirkpatrick). Serum levels greater than 1000 ng/ml occurred in 63 percent of the L.A. County series and levels above 25 ng/ml occurred in 82 percent, according to a large multiseries review. Serum carcinoembryonic antigen, commonly elevated in many adenocarcinomas, was elevated in 63 percent of the L.A. series. Detection of serum hepatitis B surface antigen was 52 percent in the L.A. series (Chlebowski et al.) and was 31 percent in the large sixth national Japanese report of 4658 primary hepatic cancers (Liver Cancer Study Group of Japan, 1987). However, the higher value for hepatitis B surface antigen in the L.A. series may be explained by the limited testing in only 62 of 121 patients. The serum hepatitis B core antibody was detected in 72 percent of the Japanese series, which more likely reflects the incidence of hepatocellular carcinoma related to hepatitis B virus (HBV) in Japan; many adults have apparently "lost" serum hepatitis B surface antigen at the time of hepatocellular carcinoma discovery.

Antemortem diagnosis is more common in the last decade and is more common in Japan because of careful screening of high risk patients and the use of newer laboratory and radiologic technics. Real time ultrasonography is useful in the detection of both hepatocellular carcinoma and of small lesions less than 2 cm in diameter (Okuda). In the Japanese series (1978-1979), 50 percent had an antemortem diagnosis and 27 percent had attempted curative surgery.

Pathogenesis. Chronic liver disease is the leading associated factor with hepatocellular carcinoma. However, the mechanism of the chronic liver disease varies around the world. On a worldwide basis, hepatocellular carcinoma occurs most frequently in the setting of chronic HBV

infection and its associated chronic liver disease (usually cirrhosis). In our experience, hepatocellular carcinoma seems to evolve in half of the chronically infected HBV patients, whereas in many other chronic liver diseases, such as Wilson's disease and primary biliary cirrhosis, evolution to hepatocellular carcinoma is unusual.

Conditions associated with the development of hepatocellular carcinoma include: HBV in the chronic infection state; cirrhosis (of many etiologies); hemochromatosis; chronic cholestatic conditions; toxins such as thorotrast and vinyl chloride; vascular diseases such as Budd-Chiari syndrome; inherited metabolic conditions such as glycogen storage disease; and certain chronic inflammatory states such as those related to parasitic infestation. In Table 7, the various associated factors in our series from the LACUSC-MC and USC Liver Unit during the years 1970-1983 are tabulated. Alcoholic cirrhosis accounts for the majority of hepatocellular carcinomas and HBV infection is especially high in the Oriental population with hepatocellular carcinoma.

In the United States, hepatocellular carcinoma is strongly associated with cirrhosis and chronic liver disease. This association varies worldwide and has changed with time. In 1888, Hanot and Gilbert reported that one-third of their patients with hepatocellular carcinoma had cirrhosis, as opposed to 25 percent noted by Rolleston and McNee of Middlesex Hospital in London in 1929. However, in the United States, 69 to 89 percent of the hepatocellular carcinomas are associated with cirrhosis. In our material, 82.1 percent of patients with hepatocellular carcinoma had cirrhosis and 10.4 percent had a normal liver (Table 7).

The development of cirrhosis is insidious; 86 percent of our patients with alcoholic or HBV-related cirrhosis had no history of prior hepatic disease at the time of tumor diagnosis. Once symptomatic, the tumor usually results in death rather quickly. However, it is likely that the tumor develops for many months or years before symptoms appear. The growth rate of hepatocellular carcinoma has been measured in many cases by ultrasound and remarkable variation is recorded. Extrapolation of the growth curve indicated that a 10 cm hepatocellular carcinoma would take from 9.8 months to 10.9 years (Sheu et al.). The lack of correlation of proliferative activity as measured by S phase growth fraction and the cytophotometric analysis of nuclear DNA of hepatocellular carcinoma also reflects the variation in biologic behavior of hepatocellular carcinoma (Kuo et al.). However, since 4.6 months are needed for a rapidly growing tumor to achieve 3 cm in diameter, a 4- to 5-month screening interval would allow for small tumor detection that is optimal for resection. Cirrhosis, which accompanies most of the HBV-related hepatocellular carinomas, develops many years earlier than the hepatocellular carcinoma. Some large regenerative nodules in the cirrhotic liver produce confusing patterns by ultrasound and may be difficult to interpret. Thus, some nontumor nodules may be resected. (See Macroregenerative Nodule.)

Radiologic Evaluation. The recent technological developments in radiographic and sonographic imaging have increased the sensitivity of hepatic tumor detection. Correlation of the angiographic pattern allows discovery of the growth pattern (Okuda et al., 1977b). Thus, confluent hepatocellular carcinoma may be

Table 7

HEPATOCELLULAR CARCINOMA* AND ASSOCIATED CONDITIONS
LACUSC Medical Center and USC Liver Unit
1970-1983

Underlying Condition	Number of Cases	Percent of Total	Sex Male:Female	Mean Age
Alcoholic cirrhosis	57	42.5	8.5:1	59.1
B viral cirrhosis and fibrosis	27	20.1	3:1	48.4
Cryptogenic cirrhosis	22	16.4	1.6:1	70.7
Cryptogenic fibrosis	10	7.5	2.3:1	62.8
Autoimmune cirrhosis	2	1.5	1:1	71.8
Primary biliary cirrhosis	1	0.7	(F)	58
Idio-portal hypertension	0	0	0	0
Hemochromatosis	0	0	0	0
Alpha-1-antitrypsin deficiency	0	0	0	0
Total chronic liver disease	119	88.8	3.6:1	56.7
Total with cirrhosis	110	82.1	3.8:1	–
Total with normal liver	14	10.4	0.6:1	–
Total with hepatocellular carcinoma	134	100	3:1	–

* In adults only, includes sclerosing hepatocellular carcinoma and fibrolamellar hepatocellular carcinoma

discerned prior to surgery. Furthermore, venous spread of hepatocellular carcinoma is detectable by ultrasound and is a guide to surgical therapy. CT evaluation revealed intrahepatic bile duct growth in 25 of 135 hepatocellular carcinomas in Japan and occurred in higher incidence than with metastatic carcinoma in Japan (Nakamura et al.).

Etiologic Factors. Hepatitis B virus is the most significant and understood risk factor for hepatocellular carcinoma development (Blumberg and London; Gerin; Kew; Popper et al.). The etiologic relationship is supported by epidemiologic, virologic, and histologic data, and by naturally occurring animal models due to similar (i.e., HBV-like) animal viruses (which share similar nucleotide sequence and produce similar pathologic hepatic lesions in susceptible hosts).

World maps of the relative incidence of chronic HBV infection and hepatocellular carcinoma are nearly interchangeable (fig. 160). These maps are based on the serum and tissue positivity for HBV infection in

Figure 160
HEPATOCELLULAR CARCINOMA
The geographic distribution of hepatocellular carcinoma (A) and hepatitis B virus surface antigen carrier (B) reveals a close correlation. (Courtesy of Professor M.C. Kew, South Africa.)

hepatocellular carcinoma patients and control groups. However, a few exceptions are noted. In Greenland, the incidence of HBV infection is high, yet the hepatocellular carcinoma rate is low in the Eskimo population (Skinhoj et al.). In contrast, in the Alaskan Eskimo population, the HBV infection rate and hepatocellular carcinoma rate are both high (Heyward et al.). In Mozambique, the incidence of HBV and chronic HBV infection are high, but the incidence of hepatocellular carcinoma is even higher than can be accounted for by the HBV rate. In Switzerland, the incidence of hepatocellular carcinoma is high (four to five times higher than the rest of Europe), yet the incidence of HBV infection is not elevated (Tuyns and Obradovic). A disparity also exists in the Asian population of the Soviet Union where the HBV infection rate is high, yet hepatocellular carcinoma is not known to be greater than the rest of Russia (Szmuness).

The virologic evidence for HBV-related hepatocellular carcinoma is based on numerous factors, including epidemiologic factors. More compelling evidence is the integration (i.e., incorporation) of the HBV genome into the host DNA of patients with chronic HBV infection. Tissue obtained by needle biopsy and autopsy has been studied by integration analysis. Multiple nodules of several hepatocellular carcinomas have been studied by integration analysis and the same integration pattern occurs in different nodules of the same patient, thus indicating monoclonal origin of hepatocellular carcinoma (fig. 161) (Esumi et al.). The cell culture of hepatocellular carcinoma has also demonstrated HBV antigen production (Alexander). However, the mechanism of oncogenesis related to HBV integration is unknown, although there appears to be a long lag period from integration to carcinoma induction. The youngest patient with hepatocellular carcinoma and apparent early HBV acquisition at birth was 8 months of age at diagnosis, but the typical latent period for hepatocellular carcinoma development is many years (Wu et al., 1987).

The histologic evidence for the HBV and hepatocellular carcinoma relationship is the association of HBV chronic liver disease with dysplasia and transition to carcinoma. Immunohistochemical studies reveal that some hepatocellular carcinoma cells produce HBV antigens, although usually the positive cells are in the nontumor liver. Hepatocellular carcinoma arises in chronic HBV infection, but the nontumor liver has progressive chronic liver disease (not persistent viral hepatitis) in the vast majority of patients. Whether the carrier state with no chronic liver disease (i.e., persistent viral hepatitis B) is a precursor of hepatocellular carcinoma remains unsettled.

The term chronic persistent hepatitis B (or persistent viral hepatitis B) has been applied in a very broad sense by some authorities as it may apply to any chronic liver disease without significant fibrosis or cirrhosis, but is due to a chronic hepatitis B infection. We have applied the term persistent viral hepatitis B (or chronic persistent hepatitis B) to the liver with no variation in regenerative activity from lobule to lobule, no portal fibrosis, no nuclear dysplasia, and uniform hepatitis B surface antigen distribution (fig. 162). In patients with persistent viral hepatitis B, we find no greater incidence of hepatocellular carcinoma than in patients with nonchronic hepatitis B and those with normal liver.

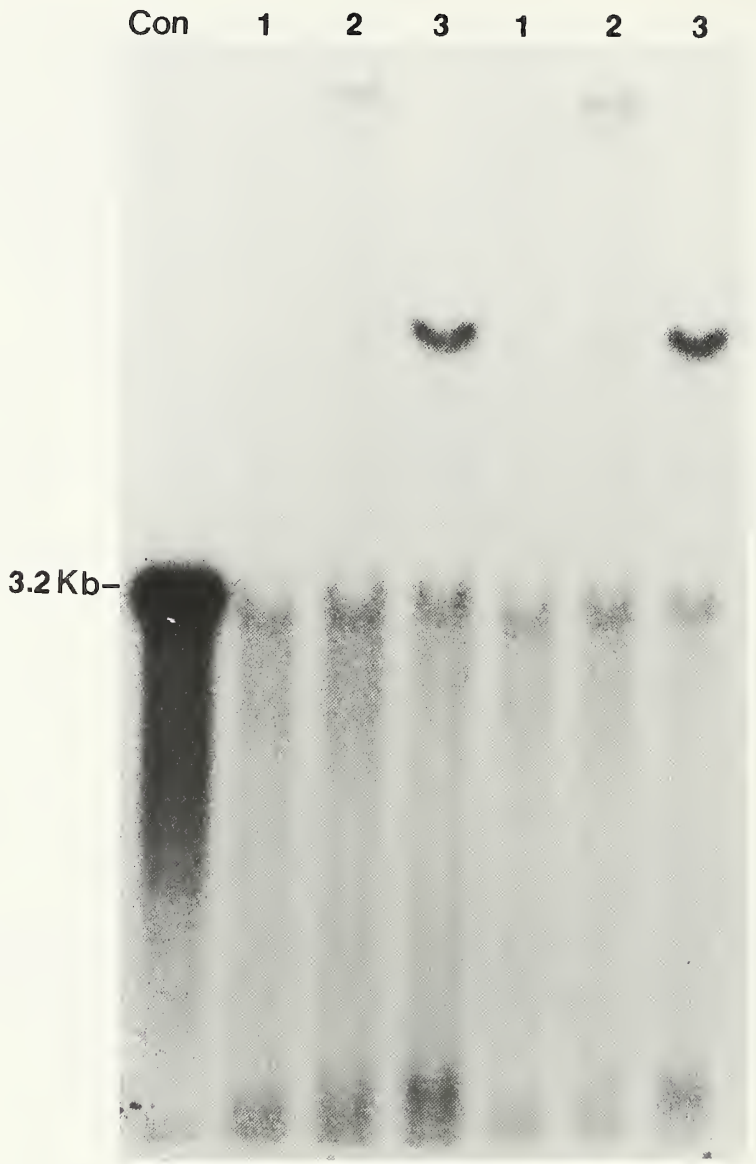


Figure 161
HEPATOCELLULAR CARCINOMA

The Western blot procedure produces bands of dark staining due to the electrophoretic separation of DNA, reactivity with HBV DNA probe, and subsequent development of probe label by radioautography. The dark lines are the bands of HBV DNA in different lengths and the similarity of bands in the different but corresponding lanes indicates monoclonality. Legend: Con for control of 3.2 Kb HBV DNA to show migration point for comparison to intact whole HBV DNA; lanes 1,2,3 are undigested, Hind III digested, and EcoRI digested DNA from one grossly apparent hepatocellular carcinoma nodule; and the second group labeled 1,2,3 are from another nodule with the same digestion sequence. The similar location of the dark bands in each set of lanes 2 and 3 indicated monoclonal origin of the two nodules. (Courtesy of Dr. S. Govindarajan, Downey, California.)

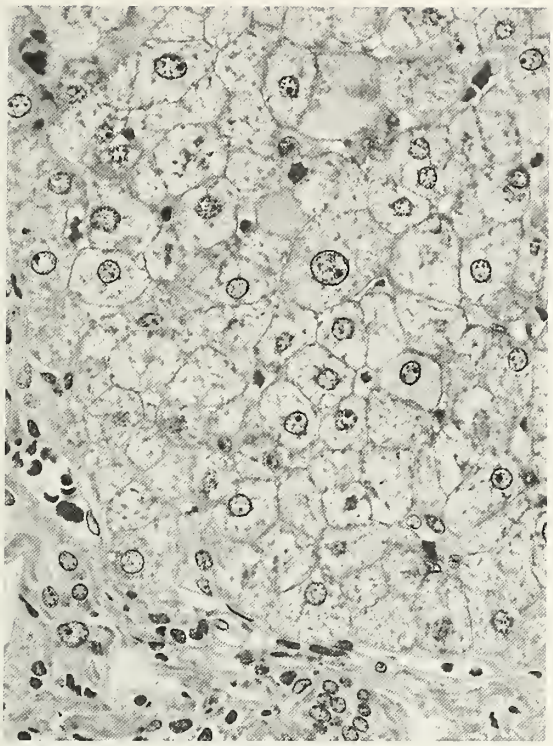


Figure 162
HEPATOCELLULAR CARCINOMA
This figure shows persistent viral hepatitis B with a uniformity of cords and scattered ground glass cells. X365.

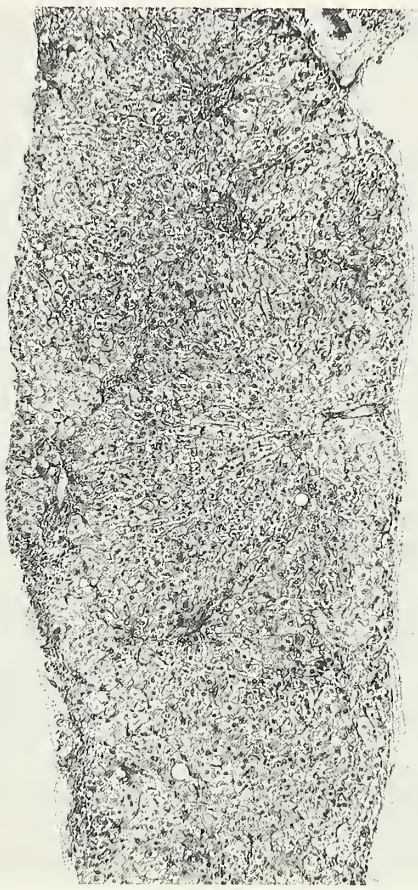


Figure 163
HEPATOCELLULAR CARCINOMA
Occult chronic active hepatitis B with no portal or lobular exudate and no fibrosis or "piecemeal necrosis" is shown. There is grade I to II nuclear dysplasia and irregular bulging of the parenchyma, reflecting irregular regeneration. X117.

In a small group of hepatocellular carcinoma patients with chronic HBV infection, the nontumor liver has irregularly distributed regenerative activity with hydropic hepatocytes, and we classify such lesions as occult (i.e., early) chronic active hepatitis B (fig. 163). Conversion of persistent viral hepatitis B to chronic active hepatitis B is known to occur, especially with the Delta hepatitis virus infection, but the role of HBV integration in this conversion is unknown.

The diagnosis of chronic hepatitis B infection is usually based on detection of serum hepatitis B surface antigen, but some patients with chronic hepatitis B have lost the serologic markers and are classified as cryptogenic cirrhosis. However, some of these patients are recognized by detection of integrated HBV DNA. Interestingly, only 14 percent of our patients with hepatocellular carcinoma and HBV infection gave a history of earlier

illness that might be interpreted as overt hepatitis, thus emphasizing the subtle and insidious character of the occult acute and chronic active viral hepatitis B.

The principal transmission of HBV, on a worldwide scale, occurs at birth; mothers who are chronic carriers pass HBV to their newborn infants who become chronic HBV carriers. Adult acquisition of HBV may also result in hepatocellular carcinoma evolution, as demonstrated in Alaskan Eskimos (Heyward et al.).

Non-A Non-B Viral Hepatitis and Other Viruses. Chronic active hepatitis following blood transfusion and occurring in the sporadic state may progress to cirrhosis and occasionally to hepatocellular carcinoma. The number of cases of cryptogenic cirrhosis with hepatocellular carcinoma (due to non-A non-B viral agent or latent chronic HBV infection) cannot be determined until a specific viral test for the non-A non-B viral agents and easier detection methods of integrated HBV are available.

Other viral agents such as hepatitis A virus, cytomegalovirus, Epstein-Barr virus, yellow fever virus, Ebola virus, Marburg virus or herpes simplex virus may induce hepatic dysfunction, but none are associated with hepatocellular carcinoma development. The Delta hepatitis virus that infects only HBV-infected patients has been examined in the chronic HBV patients and occurs at a lower rate than expected in hepatocellular carcinoma (Govindarajan et al.). This lack of correlation of Delta hepatitis virus and HBV coinfection with hepatocellular carcinoma is not yet explained.

Alcoholic Exposure. Advanced alcoholic cirrhosis is the major underlying chronic liver disease in our patients. This is typical of the United States and Western Europe where the incidence of HBV infection is lower than in the Orient. In our series, 48 percent of the cirrhotic and precirrhotic patients with hepatocellular carcinoma have alcoholic liver disease. Conversely, only 4.6 percent of the patients with alcoholic cirrhosis have hepatocellular carcinoma, and this is unchanged from the earlier time period (1918-1953), as reported by Edmondson and Steiner. However, when alcoholic cirrhosis is noted with hepatocellular carcinoma, the cirrhosis is advanced, and 10 percent have hepatocellular carcinoma. Cessation of drinking 1 or more years prior to death was reported in 21 percent of those alcoholics with advanced cirrhosis and hepatocellular carcinoma (Grases).

A review of alcoholic intake and HBV infection in patients with cirrhosis indicated that alcohol intake may promote the evolution of hepatocellular carcinoma in chronic HBV infection (Ohnishi et al.).

Hemochromatosis. In our autopsy series, 17 percent of the 41 patients with hemochromatosis developed hepatic carcinoma (either hepatocellular carcinoma or cholangiocarcinoma). The removal of iron (by phlebotomy) may not remove the risk of malignant hepatic tumor since Bomford and Williams reported that 29 percent of treated hemochromatosis patients had hepatocellular carcinoma at autopsy. Powell and associates reported that 20 percent of patients treated for hemochromatosis developed hepatocellular carcinoma. Furthermore, there is a higher risk of developing nonhepatic malignant tumors after venesection (Bomford and Williams).

Chronic Cholestatic Conditions. Chronic cholestatic conditions are rarely associated with hepatocellular carcinoma,

despite the concept that cholestasis might encourage retention of fat soluble carcinogenic compounds. Primary biliary cirrhosis has rarely been reported with hepatocellular carcinoma (Krasner et al.). Chronic cholestasis due to biliary atresia has also been associated with only a few hepatocellular carcinomas (Kulkarni and Beatty; Okuyama). Progressive familial cholestasis has also been linked to a few hepatocellular carcinomas (Dahms). One hepatocellular carcinoma in our series was in a 56 year old man who had 30 years of progressive cholestasis. He also had a younger brother with similar cholestasis.

Toxins: Thorotrast, Aflatoxin, Vinyl Chloride. Chronic exposure to plant and animal "natural" toxins as well as insecticide-herbicides has been related to hepatocellular carcinoma development. Many naturally occurring substances and poorly degradable pesticides have a carcinogenic effect if administered in intrauterine life. Thus, the toxin effect to tumor production may be very remote (Grice et al.).

The aflatoxins, a group of highly substituted coumarins produced by certain strains of the common food spoilage fungus, Aspergillus flavus, include some of the most potent hepatic carcinogens used in experimental carcinogenesis. Aflatoxins have been identified in many agricultural products, especially peanut meals and other food contaminants in concentrations that roughly parallel worldwide hepatocellular carcinoma incidence figures. In general, areas of high contamination levels of aflatoxin are also regions of high prevalence of chronic HBV infection and high hepatocellular carcinoma occurrence. The world's highest hepatocellular carcinoma rates are found in Indonesia and Mozambique. In Indonesia, a major protein source is fermented peanut cake heavily contaminated with aflatoxin; in Mozambique, aflatoxin consumption is also substantial. However, although aflatoxin consumption is carcinogenic in rats, neither a carcinogenic nor cocarcinogenic relationship in man has been proved (Lutwick). In experimental animals, there is a marked species variation in the carcinogenic effect of the aflatoxins. In general, carcinogenesis is increased when aflatoxins are consumed by malnourished subjects. In man, hepatocellular carcinoma is more common in countries where malnutrition is most severe (Patten). Aflatoxins inhibit both DNA and RNA polymerase in liver, apparently as a result of aflatoxin or its metabolite binding to chromatin. Interaction of aflatoxin with endoplasmic reticulum has been hypothesized as the mechanism of reduced protein synthesis (Wogan).

Chronic trichloroethylene exposure was claimed by two of our patients with hepatocellular carcinoma. The chronic hepatic disease in these two patients differed from alcoholic or B viral cirrhosis, but we do not know the importance of this toxin exposure.

Vinyl chloride exposure by respiratory means has been associated with hepatic angiosarcoma and hepatocellular carcinoma in man (Evans et al.; Gokel et al.). Experimental models of vinyl chloride have produced a variety of hepatic tumors.

Thorotrast, a 20 percent colloidal solution of thorium dioxide and an α-emitting substance that decays to radium and radon, is associated with hepatic angiosarcoma, cholangiocarcinoma, and hepatocellular carcinoma. Because the radioactive degradation products are retained so long, risk of malignant tumor persists throughout the life of the exposed patient

(Smoron and Battifora). Since the use of Thorotrast has been restricted in the United States, fewer cases of hepatic tumors have occurred than have been reported in many foreign countries. External radiation has not been established as a cause of hepatic tumor (Moore et al., 1976).

Hormonal medications have also been suspect for hepatic carcinogenesis. In addition to the association of oral contraceptives to hepatocellular adenomas, there is concern that oral contraceptives may also cause hepatocellular carcinomas in young women. Due to the low incidence of hepatocellular carcinoma, this potential relationship cannot be proved until more epidemiologic evidence is reviewed. In our autopsy series, during the years 1918-1959, two of nine women with hepatocellular carcinoma arising in noncirrhotic livers were in the age range of 15 to 44 years. In the same time period, 13 men had hepatocellular carcinoma in a noncirrhotic liver and four were in the age group of 15 to 44 years. In the later time period of 1960-1982, when oral contraceptives were widely used, 21 women had hepatocellular carcinoma in a normal liver and four were in the age group of 15 to 44 years. Seven of 22 men in the same age group had hepatocellular carcinoma in a normal liver (Table 8). Comparison of similar groups but with cirrhotic liver is shown in Table 9. Thus, our autopsy data reflects no relationship between hepatocellular carcinoma and oral contraceptives.

Anabolic steroid use has produced histologically appearing malignant hepatic tumors; however, these tumors are not biologically malignant. (See Anabolic Steroid-Associated Hepatocellular Adenoma.)

Exposure to unknown environmental agents may contribute to carcinogenesis during fetal development. Various plant alkaloids may cause such carcinogenesis (Schoental).

Table 8

HEPATOCELLULAR CARCINOMA IN NORMAL LIVER, MALES and FEMALES, BEFORE and AFTER 1960

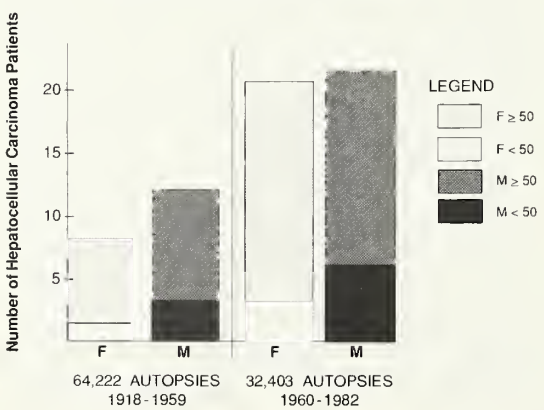
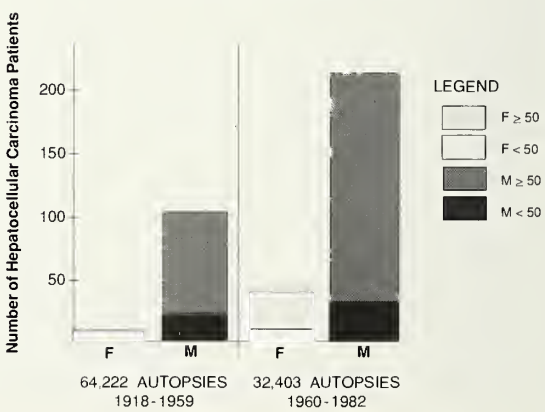


Table 9

HEPATOCELLULAR CARCINOMA IN CIRRHOTIC LIVER, MALES and FEMALES, BEFORE and AFTER 1960



Vascular Disorders (Budd-Chiari Syndrome). In South Africa, Simson reported a large series of Budd-Chiari syndrome patients with hepatocellular carcinoma. Although isolated reports existed prior to his study, Simson established a firm relationship; of 101 patients with membranous obstruction of the inferior vena cava, 48 patients had hepatocellular carcinoma. The diagnosis was based on cavography in 89 patients and autopsy in 24 patients (with both technics used in 13). In the entire hepatocellular carcinoma autopsy series of Simson, 20 percent were related to the membranous obstruction of the inferior vena cava. A relationship of hepatocellular carcinoma, vascular obstruction, and chronic HBV was noted in Pretoria because 22.8 percent of the patients with hepatocellular carcinoma and membranous obstruction of the inferior vena cava had chronic HBV, whereas the control population had an incidence of 8.7 percent. Of the hepatocellular carcinoma patients, 66 percent had chronic HBV infection and cirrhosis. The youngest patient in the membranous obstruction of the inferior vena cava series was 2 years old and the peak frequency was 31 to 40 years. A striking predominance of black patients occurred; only one white child was identified in the series. Several types of vena cava occlusion were noted, with one type being a fibrous membrane at the junction of the right atrium with the inferior vena cava. The most common type demonstrated by cavography was absence of a segment of cava. The common association of membranous obstruction of the inferior vena cava with hepatocellular carcinoma seems limited to South Africa, although occasional patients may be missed in the routine autopsy if careful dissection of the inferior vena cava and liver is not performed.

The variety of hepatocellular carcinoma microscopic patterns in the hepatocellular carcinoma/membranous obstruction of the inferior vena cava syndrome included macrotrabecular, microtrabecular, adenoid, pseudoglandular, and mixed hepatocellular/cholangiocellular. Liver biopsy of the nontumor liver allows recognition of the vascular disorder in many patients.

Metabolic and Genetic Disorders. There is remarkable variation in hepatocellular carcinoma occurring in metabolic diseases. Wilson's disease with cirrhosis has a very low incidence of hepatocellular carcinoma, even in patients with a long life span due to treatment (Kamakura et al.; Lygren). By contrast, some other metabolic hepatic disorders have a high incidence of hepatocellular carcinoma, and this includes hereditary tyrosinemia and glycogen storage disease type I. Up to 37 percent of patients over 2 years of age with glycogen storage disease type I may develop hepatocellular carcinoma (Weinberg and Finegold). In Swedish adults, α-1-antitrypsin has been associated with cirrhosis and hepatocellular carcinoma, but we have found no increased incidence of abnormal phenotypes in the hepatocellular carcinoma group compared to a control group of California patients (Eriksson and Hagerstrand; Eriksson et al.; Govindarajan et al.).

Ataxia-telangiectasia, a disease involving the cerebellum, cutaneous blood vessels, and the immune system has been associated with hepatocellular carcinoma (Kumar et al.; Yoshitomi et al.). Other malignancies associated with ataxia-telangiectasia are lymphoreticular, gastrointestinal, and mesenchymal tumors.

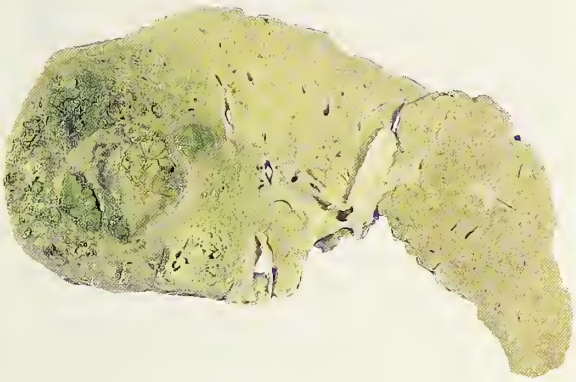
Parasitic Infestation. Although parasitic infestation is etiologically related to cholangiocarcinoma, there is less proof of parasitic influence on hepatocellular carcinoma development. Steiner reported the association of Schistosomiasis mansoni and Schistosomiasis haematobium with hepatocellular carcinoma, but no macronodular or micronodular cirrhosis common in most hepatocellular carcinomas was found. Schistosomiasis japonicum produces hepatic fibrosis, but a review of 24 Japanese patients with hepatocellular carcinoma and Schistosomiasis japonicum indicated the pattern of cirrhosis was also typical of chronic hepatitis (Nakashima et al., 1975). Serum study revealed a hepatitis B surface antigen incidence of 27 percent in the group, which was much higher than in the general population (2.5 percent). The authors concluded that HBV was more likely the cause of the hepatocellular carcinoma and cirrhosis, and that Schistosomiasis japonicum was incidental. In a later autopsy series from the same area, Schistosomiasis was noted in 32 of 232 hepatocellular carcinoma patients (13.7 percent), and two had clonorchiasis (Nakashima et al., 1983). However, the presence of the parasites in an area with such a high incidence of HBV makes proof of carcinogenesis more difficult.

Gross. Considerable variation in color, consistency, size, and growth pattern occurs with hepatocellular carcinoma. The most common hepatocellular carcinoma is golden-yellow, but large masses are a mixture of colors including green, pink, pearl-gray, red, and black. The golden areas may appear fatty and occasionally contain fat. The green color is due to bile retention, and hemorrhage produces red areas. The tumor's consistency reflects the microscopic growth pattern. A soft, smooth texture, like a ripe persimmon, usually indicates a solid growth pattern with little or no trabecular formation (fig. 164). A tumor with a dry, granular, and friable cut surface, resembling a pile rug, usually has a well-defined trabecular pattern (pl. VI-A). A hemorrhagic tumor often reflects the blood flow through widened trabeculae (pl. VI-B). White or gray reveals the extent of collagenation, duct-like transformation and less blood pooling within the trabecular growth (pl. VI-C).

Classification of the gross patterns has been attempted by numerous authorities. In 1901, Eggel proposed three categories (nodular, massive, and diffuse) based on 99 hepatocellular carcinomas in an autopsy series. However, no obvious relationship of etiology to the three categories is presently recognized. Based on a collaborative study of hepatocellular carcinoma in three different geographic areas (Los Angeles, Japan, and South Africa), a new classification has been proposed

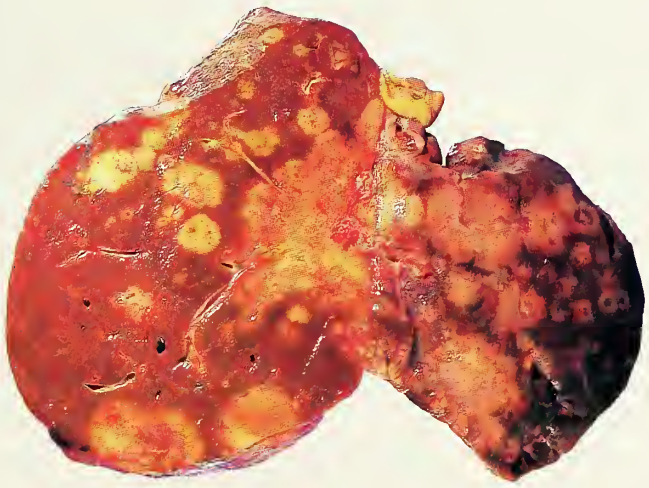
Figure 164
HEPATOCELLULAR CARCINOMA
The smooth external surface of this nodular hepatocellular carcinoma has a firm consistency.

PLATE VI
HEPATOCELLULAR CARCINOMA



A. The dry granular texture of the cut surface of a bile stained hepatocellular carcinoma is noted in this tumor that developed in a cirrhotic liver of a 95 year old Mexican woman.

B. This advanced hepatocellular carcinoma has an indeterminate growth pattern because the extensive hemorrhage, necrosis, and liver replacement by tumor obscures the original growth pattern. This is the most common gross pattern recognized in our material. This hepatocellular carcinoma arose in a Chinese man with membranous occlusion of the inferior vena cava.



C. This sclerosing hepatic carcinoma resembles cholangiocarcinoma and metastatic carcinoma. These three tumors are associated with fibrosis and typically arise in normal liver. In the areas of greatest fibrosis, the liver cells are converted to duct-like structures.

(Table 10) (Okuda et al., 1984). However, in 18 to 30 percent of cases, it is difficult at autopsy to properly classify the tumor growth pattern because of large advanced growth (pl. VI-B, pl. VII-A).

The gross appearance of the growth patterns differs in the three different geographic areas and this may also reflect and correlate with the etiologic factors. The gross features of the categories listed in Table 10 are presented by discussion of the underlying liver condition (cirrhosis or normal liver).

Cirrhotic and precirrhotic liver occur with several gross patterns of hepatocellular carcinoma. In the alcoholic patient, hepatocellular carcinoma arises not only in the fibrotic liver, but almost exclusively in the advanced cirrhotic liver. This origin for hepatocellular carcinoma in advanced alcoholic cirrhosis is not typical for HBV-related hepatocellular carcinoma, which often occurs in fibrotic liver or one that appears nearly normal. The most common pattern in all three geographic locations was the spreading hepatocellular carcinoma, which occurred in approximately one-third of the hepatocellular carcinomas in our series (figs. 165, 166). The tumor margins are indistinct and there is insidious mingling of tumor nodules with the nontumor cirrhotic nodules. Little compression of nontumor nodules is noted. Because the growth mimics cirrhosis, cirrhotomimetic growth is the term applied to the majority of the spreading hepatocellular carcinomas.

The second most common gross pattern of hepatocellular carcinoma in a cirrhotic liver is the expanding pattern, which occurred in 31 percent of the cases (figs. 167, 168). B viral cirrhosis accounts for more of this pattern than does alcoholic cirrhosis. This category corresponds to the

Table 10

HEPATOCELLULAR CARCINOMA GROSS GROWTH PATTERN

Growth Pattern	Usual Liver Condition	Percent of Cases
1. Expanding		31
A. Cirrhotomimetic		13.7
Encapsulated	Cirrhosis	
Unencapsulated	Cirrhosis	
B. Pseudoadenomatous	Normal liver	16
C. Sclerosing		1
Diffuse	Normal liver	
Septate	Normal liver	
2. Spreading	Cirrhosis	34
A. Cirrhotomimetic	Cirrhosis	30
B. Invasive with fibrosis	Cirrhosis or normal	4
3. Multifocal and diffuse	Cirrhosis	12
4. Indeterminate	Indeterminate	23

Figure 165
HEPATOCELLULAR CARCINOMA
A spreading hepatocellular carcinoma in a B viral cirrhosis of a 60 year old man with no symptoms was incidentally discovered because of elevated serum transaminase and positive serum for hepatitis B surface antigen. The tumor is nodular and spreads into the poorly defined nodules of the surrounding cirrhotic liver.

"massive" category proposed by Eggel. The principal feature of these tumors is that they compress and displace the surrounding parenchyma, similar to metastatic carcinoma. The tumor nodules usually mimic the underlying cirrhosis growth pattern as well. For example, in the coarsely nodular liver with hepatocellular carcinoma, the tumor nodules are discrete, but in the alcoholic cirrhosis with poorly defined nodules (pseudolobular), the tumor nodules are less easily recognized. The pedunculated hepatocellular carcinoma fits into this category (fig. 169). Encapsulated cirrhotomimetic hepatocellular carcinoma arises almost exclusively in a cirrhotic liver and is common in Japan, but less common in the United States and South Africa. The capsule does not seem to be condensed stroma due to expansile growth, since very small hepatocellular carcinomas may also be encapsulated. Satellite nodules, which are encapsulated, may occur around an encapsulated hepatocellular carcinoma (pl. VII-A).

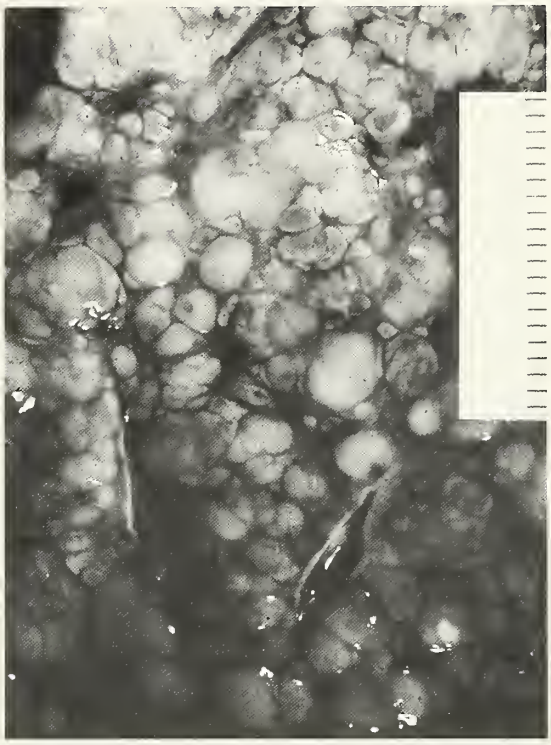


Figure 166
HEPATOCELLULAR CARCINOMA
A spreading hepatocellular carcinoma with nodular pattern occurred in a 58 year old alcoholic man admitted for ascites. The pale white nodules are hepatocellular carcinoma, but almost all nodules are involved. (Fig. 4 from Hepatocellular Carcinoma, p. vii. Okuda, K. and Peters, R.L. [Eds.]. New York: John Wiley & Sons, 1976.)

Multifocal growth pattern comprises 10 to 20 percent of the series and almost all arise in cirrhosis (pl. VIII-A). This pattern is typical of hepatocellular carcinoma in hemochromatosis. This category usually has at least two, and usually several, remotely isolated tumor foci of equal size without a clear large primary site. This pattern is likely due to a single hepatocellular carcinoma with diffuse intrahepatic spread, and sampling multiple nodules by HBV integration patterns supports this interpretation. There is an abundance of

Figure 167
HEPATOCELLULAR CARCINOMA
This is a spreading hepatocellular carcinoma with clear color distinction of pale tumor and dark liver without tumor. (Courtesy of Dr. Ian Simson, Pretoria, South Africa.)

Figure 168
HEPATOCELLULAR CARCINOMA
This spreading hepatocellular carcinoma is a large mass composed of smaller nodules, but is expanding and compressing the adjacent cirrhotic liver. A few nodules of hepatocellular carcinoma outside the mass are a slightly different color than the large mass. As the hepatocellular carcinoma grows and replaces the nontumor liver, the distinction of spreading and expanding hepatocellular carcinoma becomes impossible.

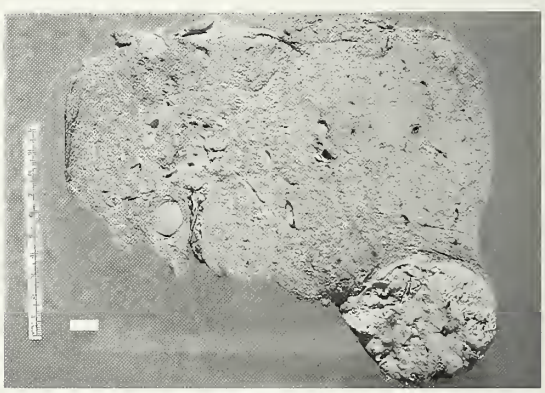


Figure 169
HEPATOCELLULAR CARCINOMA
A pedunculated, expanding hepatocellular carcinoma occurred in a 58 year old man with alcoholic cirrhosis. There is a fine pseudolobular pattern of the cirrhosis, similar to the growth pattern of the hepatocellular carcinoma.

sinusoidal and portal vein branch invasion noted in most hepatocellular carcinomas. Most multifocal hepatocellular carcinomas are incidental findings in patients who died with cirrhosis and apparent hepatic failure (fig. 170). In some examples, multifocal hepatocellular carcinoma is also diffuse or disseminated. Eggel labelled this pattern "diffuse" and reported it in 6 percent of his cases (figs. 171-173).

Spreading infiltrative hepatocellular carcinoma, which occurs predominantly in alcoholic cirrhotic livers is another gross pattern of growth. The tumor nodules efface the cirrhotic structure and the tumor margin with nontumor is very vague. The gray scar-like areas are due to fibrosis of the invasive tumor. These tumors often have duct-like transformation, as revealed by light microscopy (fig. 174).

Normal liver is associated with two growth patterns—pseudoadenomatous and sclerosing. Pseudoadenomatous hepatocellular carcinoma is a homogenous mass that expands and appears similar to an adenoma (pl. VII-B; fig. 175). As the tumor enlarges, hemorrhage alters the central area. Perhaps some of these hepatocellular carcinomas arise in adenomas and traceability to benign hepatocellular adenoma is destroyed. This type of hepatocellular carcinoma may disseminate within the liver and form masses of similar size. This is the common pattern in glycogen storage disease type I.

Sclerosing expanding hepatocellular carcinoma is the second most common pattern arising in a normal liver. There are two subtypes—diffuse and septate. The diffuse group resembles metastatic carcinoma and cholangiocarcinoma (pl. VI-C) by gross and light microscopic appearance. The septate subgroup resembles focal nodular hyperplasia because of the irregular sclerosis and bulging nodularity. This is the common pattern for fibrolamellar hepatocellular carcinoma (fig. 176).

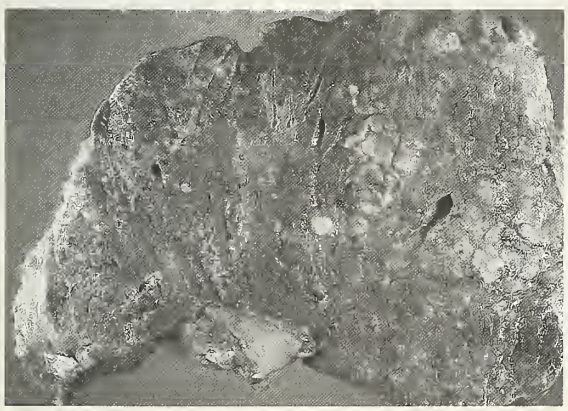


Figure 170
HEPATOCELLULAR CARCINOMA
This incidental multifocal hepatocellular carcinoma in an alcoholic cirrhotic patient has intrahepatic portal vein invasion. The multiple nodules of white tumor contrast with the dark cirrhosis.

Figure 171
(Figures 171-173 are from the same patient)
HEPATOCELLULAR CARCINOMA
This diffuse hepatocellular carcinoma on cut surface appears to be only a cirrhotic liver. Uniform nodules are hepatocellular carcinoma and almost entirely neoplastic.

Figure 172
HEPATOCELLULAR CARCINOMA
The gross cut surface shows relative uniform nodularity and similar color of all the bulging, light yellow nodules of the hepatocellular carcinoma in figure 171.

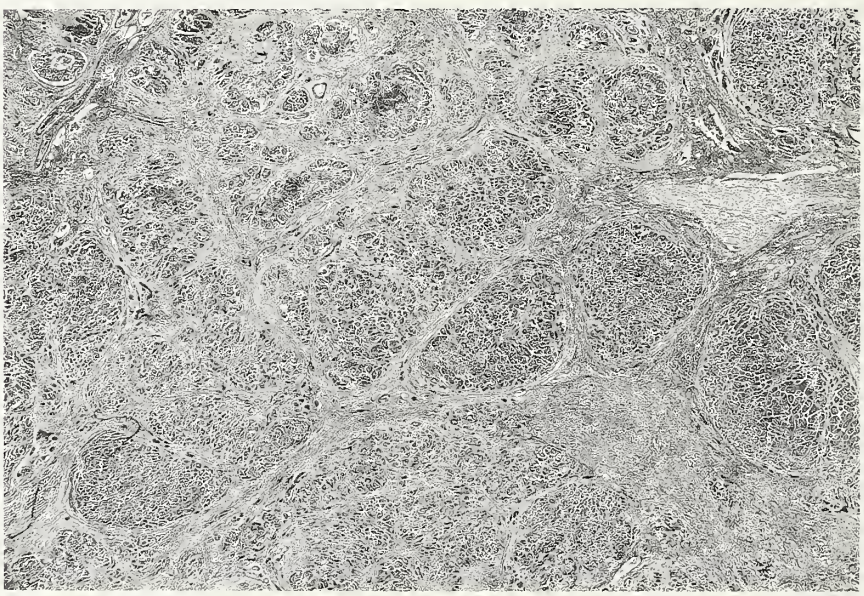
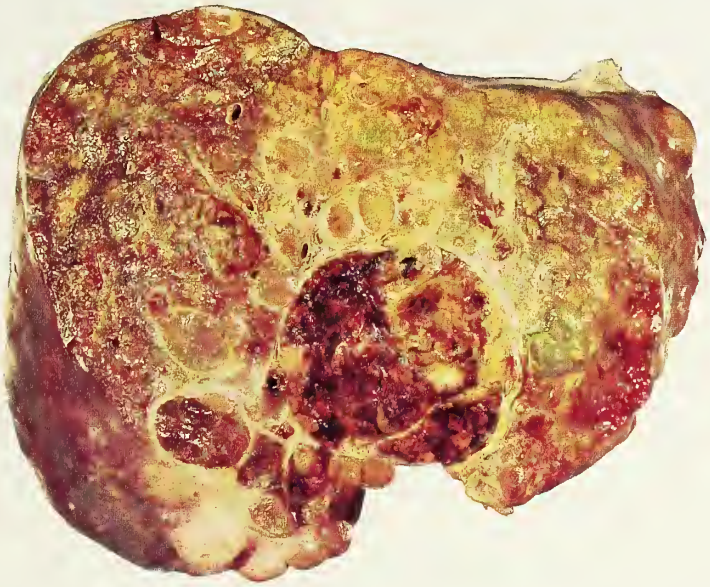
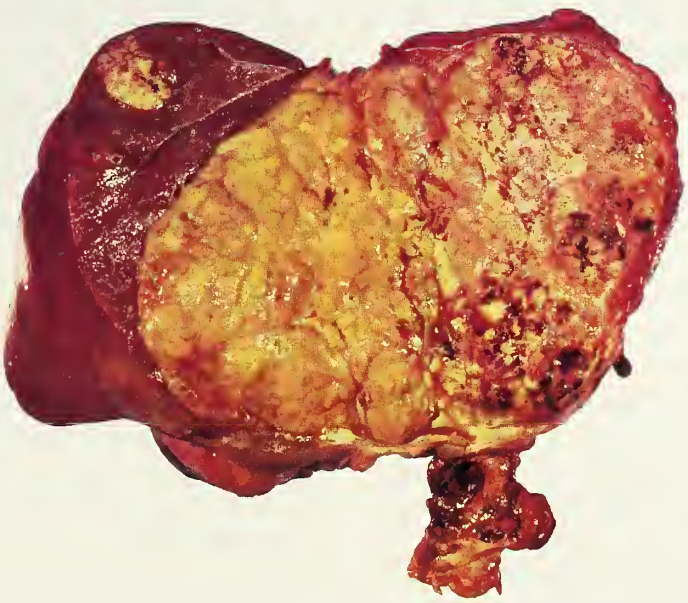


Figure 173
HEPATOCELLULAR CARCINOMA
The diffuse hepatocellular carcinoma has a cirrhotomimetic growth pattern with nodules of tumor separated by fibrous bands. X10.

PLATE VII
HEPATOCELLULAR CARCINOMA



A. An encapsulated hepatocellular carcinoma in the cirrhotic liver of a 72 year old man has spread throughout the liver making the expanding character inapparent. (Pl. I-A from Fascicle 25, First Series.)



B. The pseudoadenomatous pattern of this hepatocellular carcinoma with extensive necrosis is a large mass and arose in a normal liver. (Pl. I-B from Fascicle 25, First Series.)

Figure 174
HEPATOCELLULAR CARCINOMA
The fibrosing hepatocellular carcinoma expands and invades adjacent nodules of the cirrhotic liver, with loss of the nodular tumor pattern. The white tubular structures are from arterial injection with barium.

Figure 175
HEPATOCELLULAR CARCINOMA
A pseudoadenomatous pattern of hepatocellular carcinoma developed in a previously normal liver. The main tumor mass is fairly uniform, soft, and nonnodular.

Figure 176
(Figures 176 and 223-225 are from the same patient)
HEPATOCELLULAR CARCINOMA
An expanding hepatocellular carcinoma with septate fibrosis resembles focal nodular hyperplasia because of the central scar and radiating septa that divide the tumor into segments. This is typical of fibrolamellar hepatocellular carcinoma. (Courtesy of Dr. Edward Smith, Jackson, Mississippi.)

Minute hepatocellular carcinomas (less than 2 cm) are too small to classify by these growth criteria (pl. VIII-B; fig. 177). Occasionally, they will invade the portal venous system, even though the primary site is not recognizable. Sometimes the hepatic ducts are filled with hepatocellular carcinoma and no primary focus can be found. In approximately one-quarter of these, the growth pattern is not recognizable as one of the above mentioned categories. These hepatocellular carcinomas are considered of indeterminate pattern (pl. VI-B) due to the tumor growth obliterating the underlying liver architecture.

Dysplasia and Paraplasia. Many chronic hepatic diseases that antedate hepatocellular carcinoma have foci of

Figure 177
(Figures 177 and 200
are from the same patient)
HEPATOCELLULAR CARCINOMA
This minute hepatocellular carcinoma has a slight variation in color, which is also a feature of hepatocellular adenoma. This tumor occurred in a chronic alcoholic without recognized liver disease. (Courtesy of Drs. Lillian Rowan and Robert Rosser, Burbank, California.)

altered growth that form nodules distinct from simple regeneration. The hepatocytes within these nodules proliferate and expand and often compress the adjacent hepatocytes (fig. 178). We refer to these nodules as paraplastic nodules (figs. 179-181). The paraplastic hepatocytes have regular nuclei, finely divided chromatin, and prominent nucleoli, but rarely have mitoses or enlarged nuclei, as occur in carcinoma. In experimental animals given hepatic carcinogens, areas similar to paraplastic nodules have elevated γ-glutamyl transferase activity, as do malignant hepatocytes (Cameron et al.). However, Uchida and associates were unable to identify similar enzyme staining of paraplastic nodules in a human liver with hepatocellular carcinoma.

Perhaps the most extreme example of paraplasia is the development of multiple hepatic adenomata in glycogen storage disease type I (fig. 182). In this disorder, the paraplastic nodules are one lobule in size, and as they continue to enlarge to several lobules, the term adenoma is applied. As hepatocellular dysplasia occurs within the paraplastic nodule (or small adenoma), malignant transition occurs. Often the microscopic distinction between adenoma and carcinoma is difficult. The transition from adenoma to carcinoma may be very subtle as both have a trabecular growth pattern and the increased nuclear/cytoplasmic ratio of hepatocellular carcinoma may not be very discernible. Formation of a microtrabecular growth pattern (thick cords) is a criterion of hepatocellular carcinoma.

With the marked increase in hepatocellular adenoma due to oral contraceptives in recent years, transition of adenoma to carcinoma has been of special concern. However, studies of such patients requires control groups of similar age, as a few patients on oral contraceptive agents will incidentally develop hepatocellular carcinoma.

Liver cell dysplasia is recognized by clusters of hepatocytes with large nuclei and cytoplasm. Such changes are common in B viral cirrhosis with hepatocellular carcinoma, but less common in hepatocellular carcinoma arising in alcoholic cirrhosis or other chronic hepatic diseases. Anthony and associates noted that 64.5 percent of African patients with hepatocellular carcinoma arising in cirrhotic livers had liver cell dysplasia in nontumor parts of the liver, whereas similar liver cell dysplasia was noted in only 20.3 percent of cirrhotic livers without hepatocellular carcinoma, and only 1 percent of normal livers in the same population. There is little evidence that the dysplastic hepatocytes

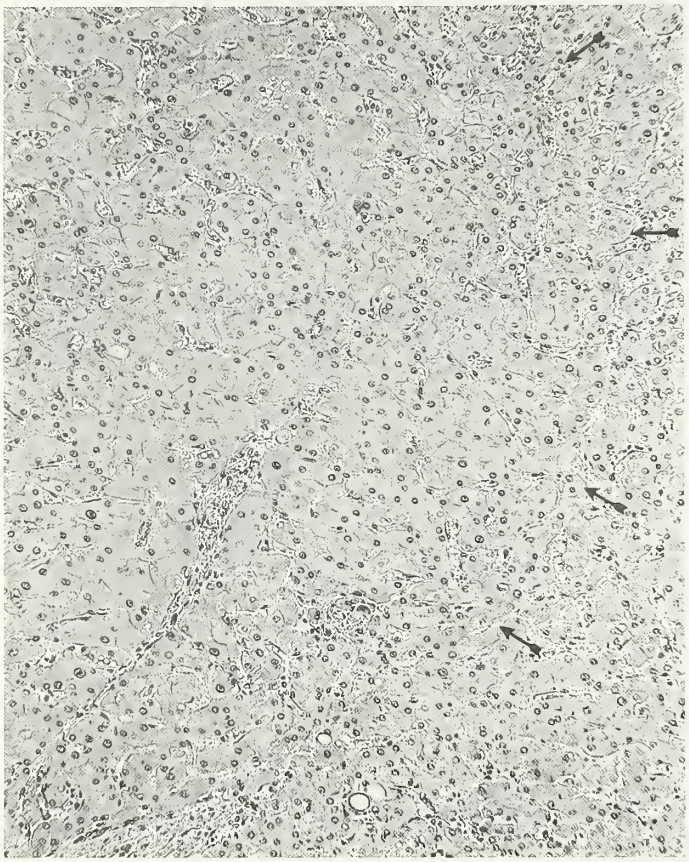


Figure 178
HEPATOCELLULAR CARCINOMA
A nodular growth pattern termed paraplasia is recognized by the bulging and expansive growth of the central hepatocytes. The margins are "pushed" by the slightly larger hepatocytes (arrows). X120.

Figure 179
HEPATOCELLULAR CARCINOMA
This figure shows a paraplastic growth pattern with bulging, nodule-producing, elongated hepatocytes outside the nodule. This paraplasia is present in a cirrhotic liver with hepatocellular carcinoma in other regions of the liver. X117.

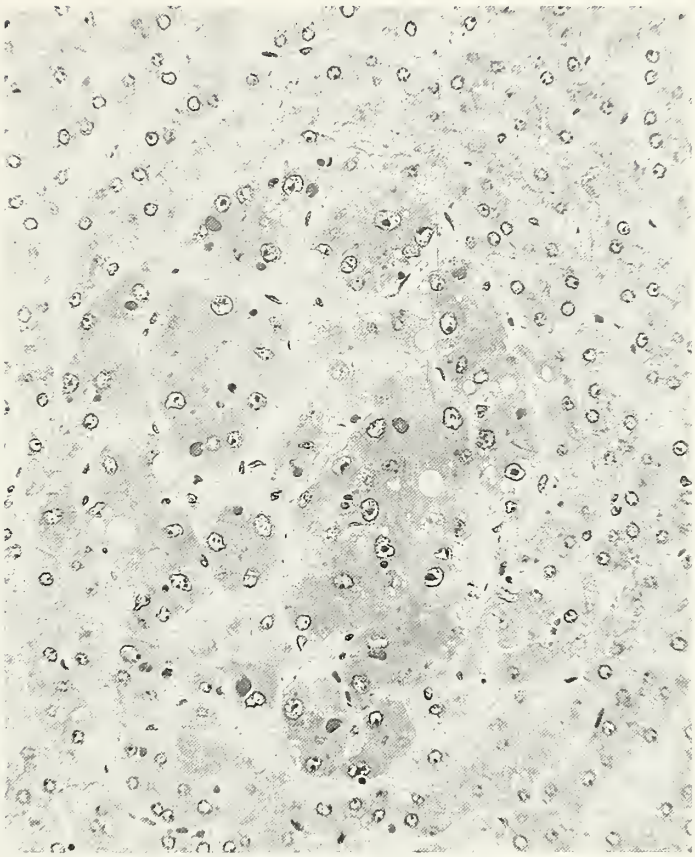


Figure 180
(Figures 180 and 202
are from the same patient)
HEPATOCELLULAR CARCINOMA
The paraplastic nodule has areas of hepatocytes that are larger and have more prominent nuclei, and thus are probably hepatocellular carcinoma. X235.

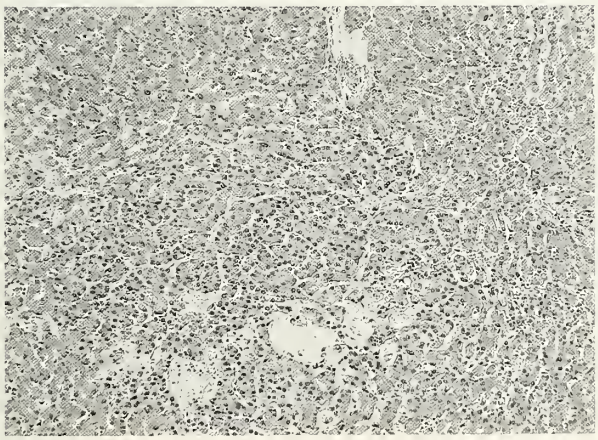


Figure 181
HEPATOCELLULAR CARCINOMA
This figure shows paraplastic growth with a trabecular growth area in the center and wider cords than the adjacent liver. The central area is a trabeculae of hepatocytes with more prominent nuclei and probably is hepatocellular carcinoma. There are prominent vascular spaces at the margin of the transition area. X70.

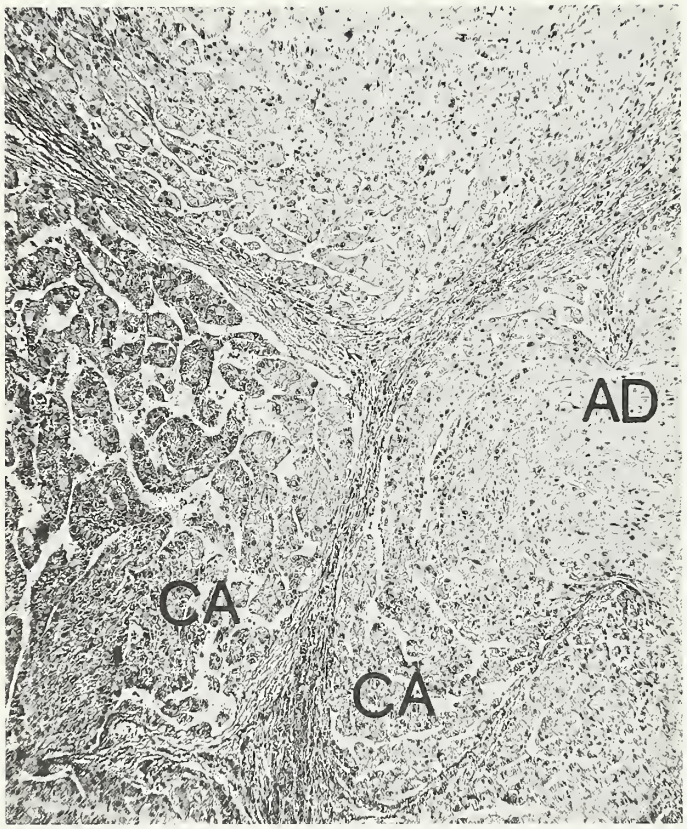


Figure 182
(Figures 182 and 221
are from the same patient)
HEPATOCELLULAR CARCINOMA
This low grade (I) hepatocellular carcinoma (CA) with hepatocellular adenoma (AD) with a microtrabecular pattern developed in a patient with glycogen storage disease type I. X70. (Courtesy of Dr. Rodney Howell, Houston, Texas.)

are premalignant in spite of their bizarre appearance. Usually, zones of dysplastic hepatocytes are crescentic or concave on one side and appear to be displaced by more rapidly proliferating paraplastic hepatocytes (not dysplastic). The dysplastic cells may reflect aberrant biologic activity and not necessarily greater proliferative activity.

Microscopic. The microscopic appearance of hepatocellular carcinoma is highly variable between different tumors and within the same tumor. Multiple sections must be examined to properly classify large tumors. One block for each centimeter in diameter of the major mass is recommended for accurate classification. Prognosis of some tumors with a mixed pattern is best predicted by the most malignant component. For example, hepatocellular carcinoma of the fibrolamellar type, which has a better prognosis than the usual hepatocellular carcinoma, may be mixed with areas of trabecular hepatocellular carcinoma of the typical variety in which the prognosis is poor. Thus, in this example of hepatocellular carcinoma with multiple patterns, the prognosis is related to the nonfibrolamellar hepatocellular carcinoma. Furthermore, certain histologic patterns are more common in hepatocellular carcinomas arising in cirrhosis than in normal liver.

The biologic factors that contribute to the histologic pattern include: (1) the relationship of the tumor to the nontumor liver; (2) the relationship of tumor cells to each other (i.e., their cohesiveness and tendency toward organoid arrangement); (3) the relationship of tumor to stroma and inflammatory reaction; (4) the relationship of tumor cells to vascular supply; and (5) the cytologic features of the tumor cells.

The relationship of the tumor to the nontumor liver is usually noted by the bulging nodule of tumor extending into other liver nodules (figs. 183, 184). Even in spreading hepatocellular carcinoma, the tumor foci form nodules that enlarge within nontumor liver tissue. Occasionally, a fibrous capsule is formed (fig. 185). Tumor spread into the hepatic sinusoids was reported by Nakashima and associates (1983), but

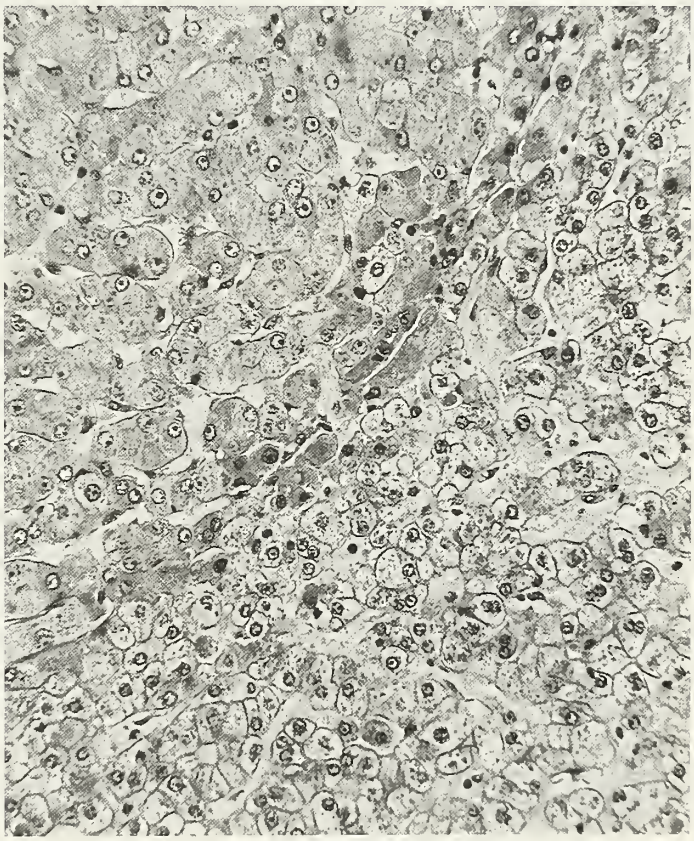


Figure 183
HEPATOCELLULAR CARCINOMA
Grade I hepatocellular carcinoma (upper left) compresses the hepatocellular adenoma (lower right). A finely granular brown pigment that resembles Dubin-Johnson pigment is present. X234. (Courtesy of Dr. Robert Cardelli, Santa Clara, California.)

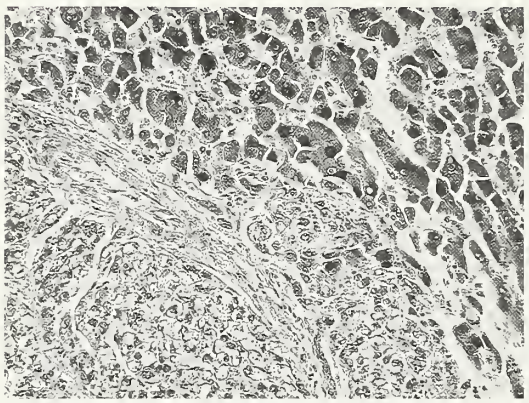


Figure 184
HEPATOCELLULAR CARCINOMA
The bulging margin (lower left) of this hepatocellular carcinoma with B viral cirrhosis shows positive staining (brown) of the nontumor hepatocellular cytoplasm by immunoperoxidase technic for anti-HBs; the hepatocellular carcinoma did not stain. Immunoperoxidase with anti-HBs. X117.

occurred only in some poorly differentiated hepatocellular carcinomas. In our experience, sinusoidal tumor spread is more common in metastatic carcinoma than hepatocellular carcinoma. Spread of hepatocellular carcinoma into the portal vein and the hepatic vein is relatively common, especially in cirrhosis (pl. VIII-C).

Tumor cell relationship is reflected in the cohesiveness and tubular growth structures, which are enveloped by an endothelial lining. This pattern, if cut longitudinally, is trabecular. A microtrabecular pattern is noted if the cell plates are less than eight cells in thickness, whereas a macrotrabecular pattern is thicker (fig. 186). Necrosis occurs in some macrotrabeculae, which forms a gland-like space that mimics metastatic adenocarcinoma (fig. 187). An acinar or pseudoglandular pattern occurs if there is a small lumen (a canaliculus), which often contains bile (figs. 188, 189).

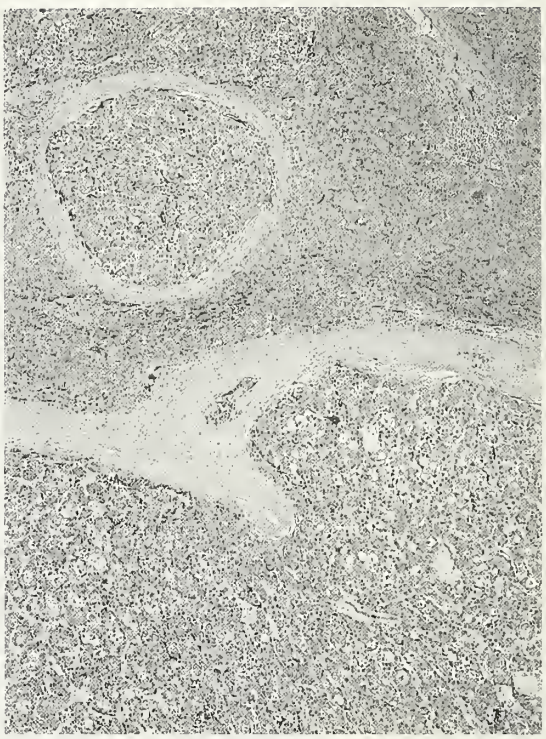


Figure 185
HEPATOCELLULAR CARCINOMA
This encapsulated hepatocellular carcinoma in a noncirrhotic liver has a thick fibrous capsule around the tumor. A separate encapsulated hepatocellular carcinoma nodule is located in the adjacent parenchyma. X125. (Courtesy of Dr. James Shorey, Dallas, Texas.)

The vascular supply of hepatocellular carcinoma is abundant in most tumors and the trabeculae are sheathed by endothelial cells (fig. 190). The surrounding space is analogous to the sinusoidal spaces and carries arterial blood. Some hepatocellular carcinomas grow in solid sheets with few vascular channels and resemble squamous carcinoma. This pattern is called compact or solid type, and if only a small fragment of well-differentiated hepatocellular carcinoma is available, distinction from regenerating liver may be difficult.

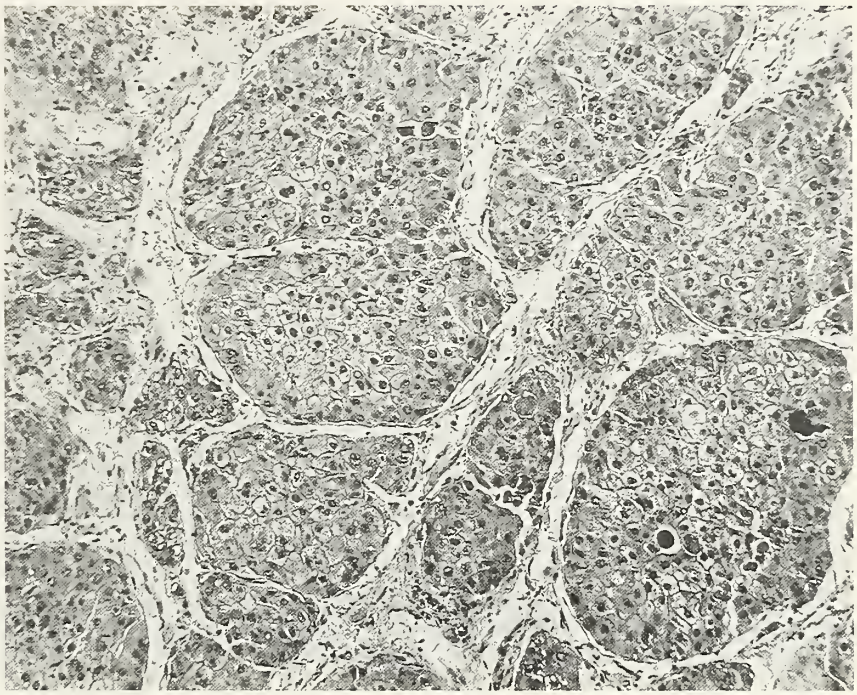


Figure 186
HEPATOCELLULAR CARCINOMA
Macrotrabecular hepatocellular carcinoma has large, thick trabeculae. No canaliculi are visible in these cords. X117.

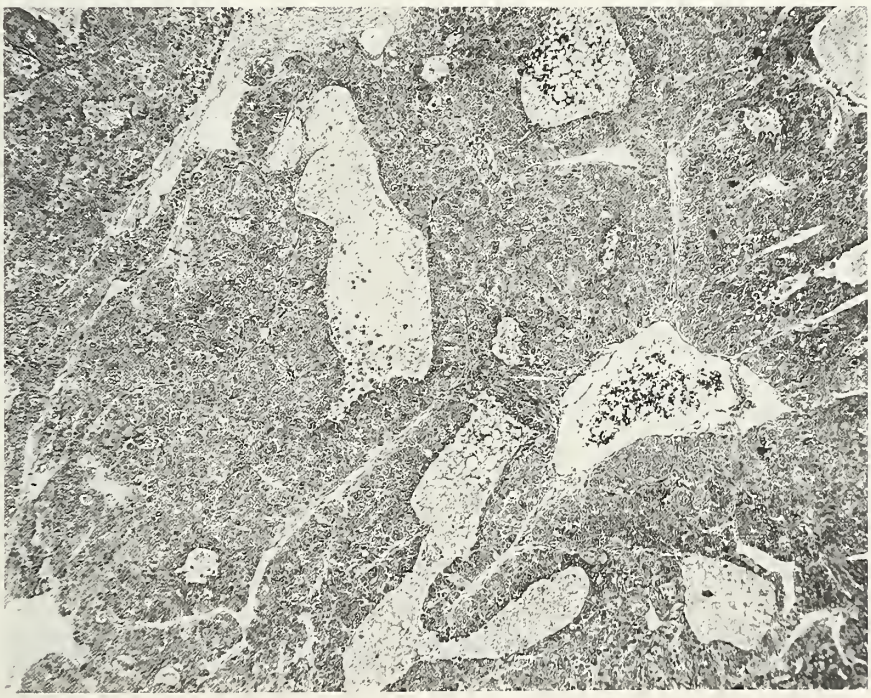


Figure 187
HEPATOCELLULAR CARCINOMA
Macrotrabecular hepatocellular carcinoma may have cystic necrosis that merges into a glandular pattern, often with necrotic debris that mimics adenocarcinoma, within the lumen. X40. (Courtesy of Prof. J.B. Gibson, Hong Kong.)

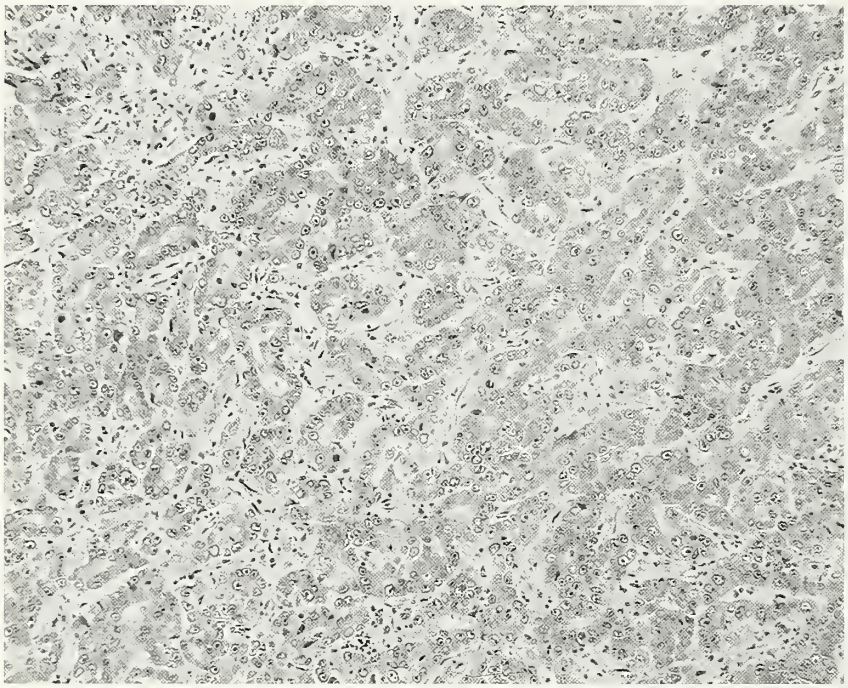


Figure 188
(Figures 188 and 189 are from the same patient)
HEPATOCELLULAR CARCINOMA
A mixed trabecular-acinar pattern of hepatocellular carcinoma has interstitial spaces that contain some connective tissue and dilatation of the canaliculi. X225. (Courtesy of Dr. Chynel Henning, Long Beach, California.)

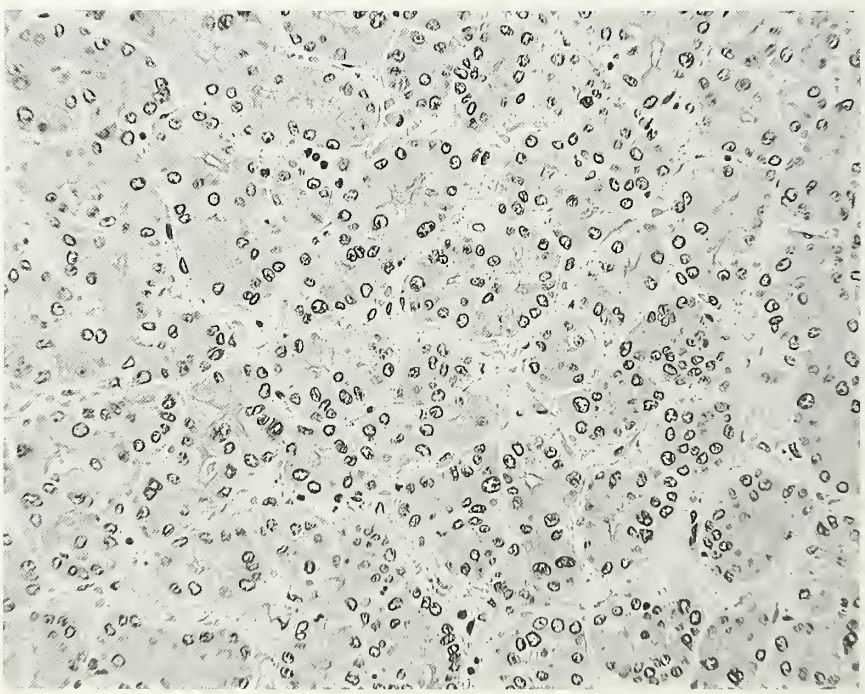


Figure 189
HEPATOCELLULAR CARCINOMA
A cross section of acinar structures composed of polygonal cells with round nuclei is illustrated. X225. (Courtesy of Dr. Chynel Henning, Long Beach, California.)

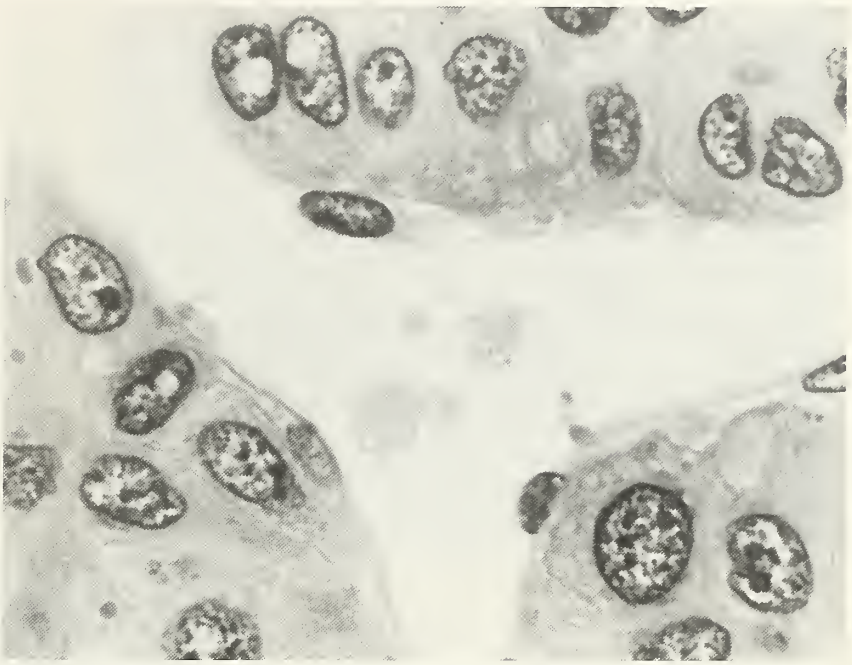


Figure 190
(Figures 190, 198, and 201 are from the same patient)
HEPATOCELLULAR CARCINOMA
The endothelial cells cover the trabeculae of most hepatocellular carcinomas, as noted in this figure. X1000.

Stromal components of most hepatocellular carcinomas are minimal, but some tumors incite a stromal reaction in the vascular component (fig. 191). The collagen seems to promote a tubular or acinar pattern, which may become more glandular in appearance (figs. 192, 193). The trabecular with glandular transformation, adenoid, and papillary hepatocellular carcinomas are other distinctive histologic patterns. In about 12 percent of our hepatocellular carcinomas, some trabecular areas had a glandular transformation. A small number of hepatocellular carcinomas have a marked glandular dilatation that resembles a thyroid acinus (adenoid pattern), as seen in figure 194. Rarely, a papillary pattern will be noted as one of several patterns (fig. 195). These histologic patterns do not alter the prognosis, but with selected material on a small sample, the variation in pattern may result in a misdiagnosis of metastatic carcinoma. Various degrees of sclerosis occur, and if abundant in numerous sections, the term sclerosing hepatocellular carcinoma is applied. Sclerosing hepatocellular carcinomas account for less than 2 percent of all hepatocellular carcinomas.

The grading of hepatocellular carcinoma has been correlated with prognosis, clinical parameters, and laboratory tests. The criteria for grading include: degree of cytoplasmic acidophilia; nuclear chromatism; nuclear/cytoplasmic ratio; cell cohesiveness; cell function (bile production); and histologic architecture. Grade I hepatocellular carcinoma is recognized as the most benign area of hepatocellular carcinoma (fig. 183). The nuclear/cytoplasmic ratio is nearly normal and is recognized by the overall growth pattern (bulging nodule

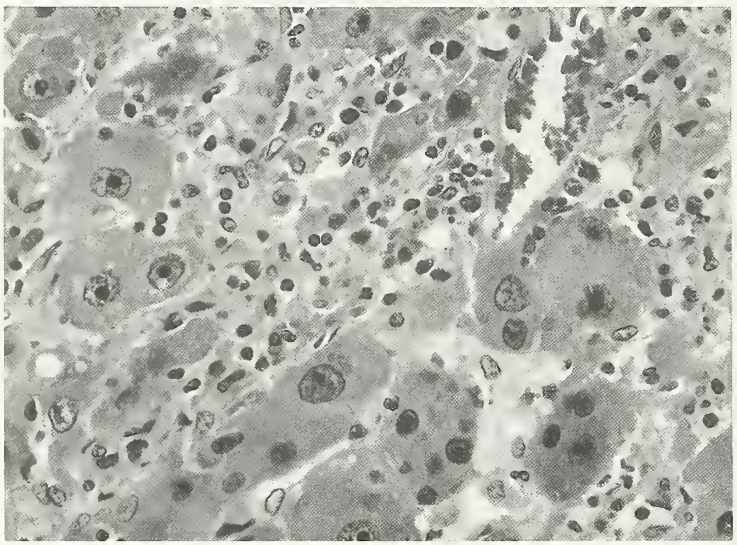


Figure 191
HEPATOCELLULAR CARCINOMA
A grade III hepatocellular carcinoma has marked lymphocytic infiltration, which is unusual and of no known significance. The moderate variation in cell and nuclear size as well as a larger cell size account for the grade III classification. X1240.

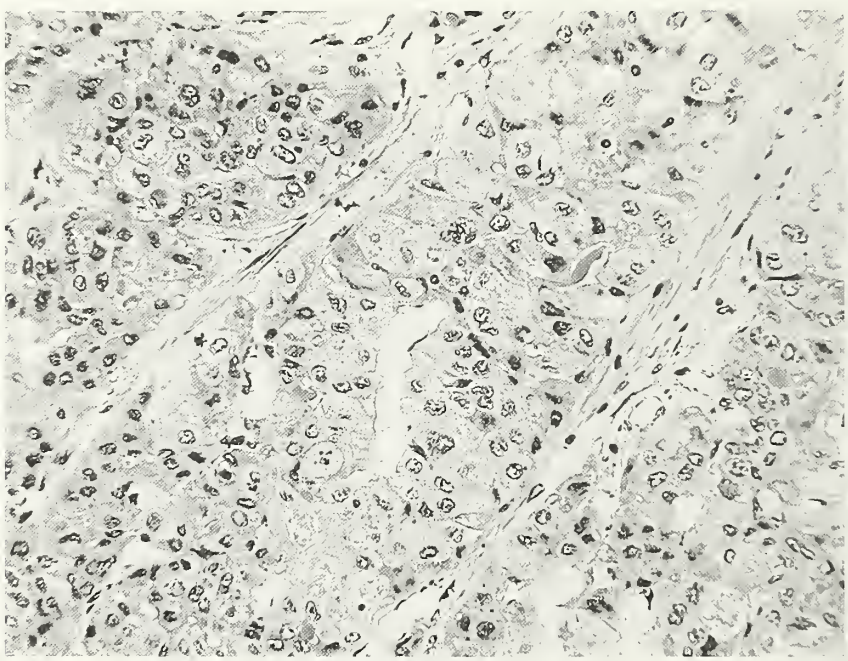


Figure 192
HEPATOCELLULAR CARCINOMA
Fibrosis and a mixture of duct-like and trabecular hepatocellular carcinoma may be mistaken for adenocarcinoma. X235. (Courtesy of Dr. Chynel Henning, Long Beach, California.)

Figure 193
HEPATOCELLULAR CARCINOMA
This hepatocellular carcinoma arose within an adenoma of a young woman on oral contraceptives. The hepatocellular carcinoma has a macrotrabecular growth pattern (lower left) in contrast to the nearly solid appearance of the adenoma. X85. (Courtesy of Dr. Luis Balart, New Orleans, Louisiana.)

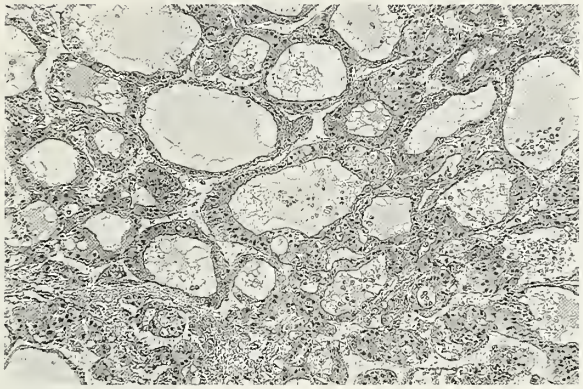


Figure 194
HEPATOCELLULAR CARCINOMA
The adenoid pattern of hepatocellular carcinoma has markedly dilated acini often with central pink staining material. X70.

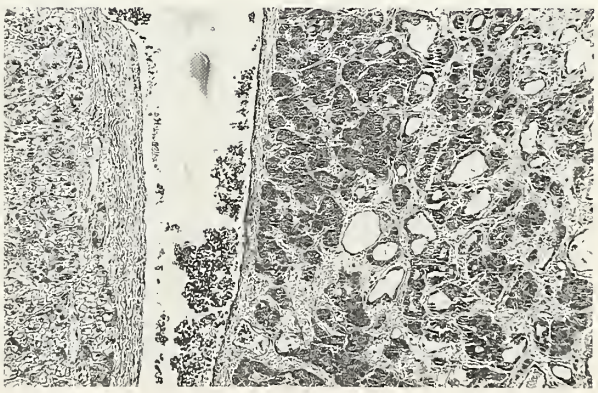


Figure 195
HEPATOCELLULAR CARCINOMA
This field of hepatocellular carcinoma has a variety of patterns including clear cell next to a large vessel, trabecular, adenoid, and acinar patterns. Distinction of each pattern is arbitrary, as they merge together well in this example. X70.

formation and compression of adjacent cords). A pure grade I hepatocellular carcinoma is recognized by its behavior (i.e., metastasis of what was considered hepatocellular adenoma) or relationship to surrounding tissue (i.e., vein invasion, and most commonly, its association with other areas of grade II hepatocellular carcinoma). Grade II hepatocellular carcinoma has larger, more hyperchromatic nuclei, more eosinophilic cytoplasm, and acini (fig. 196); in addition, trabeculae and papillae may be formed (figs. 197-199). Grade III hepatocellular carcinoma has larger hyperchromatic and more variable nuclei with multiple nucleoli and comparatively less cytoplasm (fig. 191). There may be loss of trabecular arrangement and syncytial giant cells are more numerous. Bile plugs are less evident. Grade IV hepatocellular carcinoma has less mature cells with large nuclei and may have little cytoplasm. This tumor grade may be hard to recognize as hepatocellular in origin. Trabeculae are rare and intravenous invasion may be solid tumor. Bile plugs are rare. Many hepatocellular carcinomas also have more than one grade of tumor, often separated by a thin fibrous septae.

Intracellular inclusions in hepatocellular carcinoma are: alcoholic hyalin; pale bodies; α-1-antitrypsin bodies; and hyaline bodies.

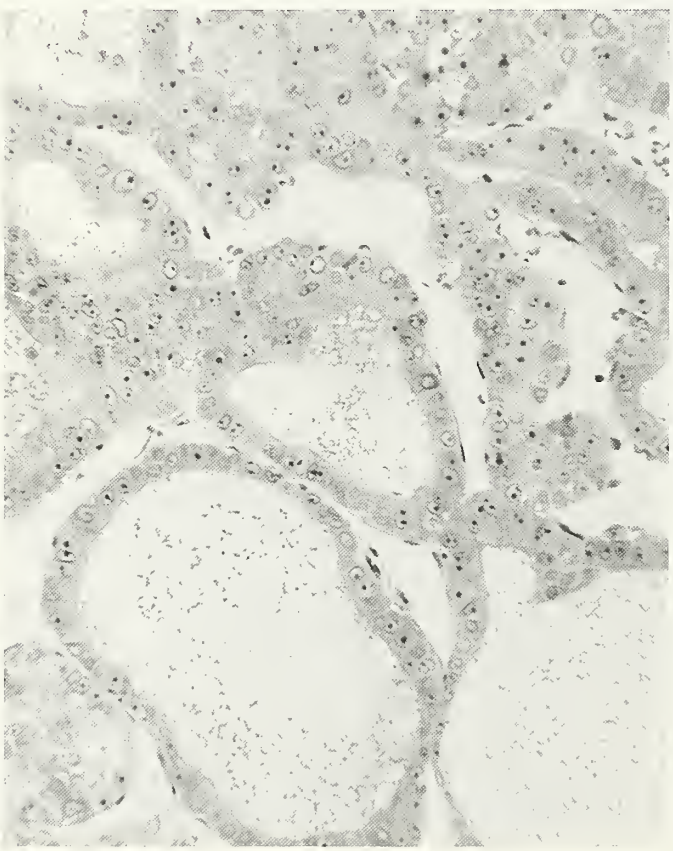


Figure 196
HEPATOCELLULAR CARCINOMA
The adenoid pattern of hepatocellular carcinoma (with dilated acini) may have markedly dilated spaces and mucin production may be noted within the lumen. X585.

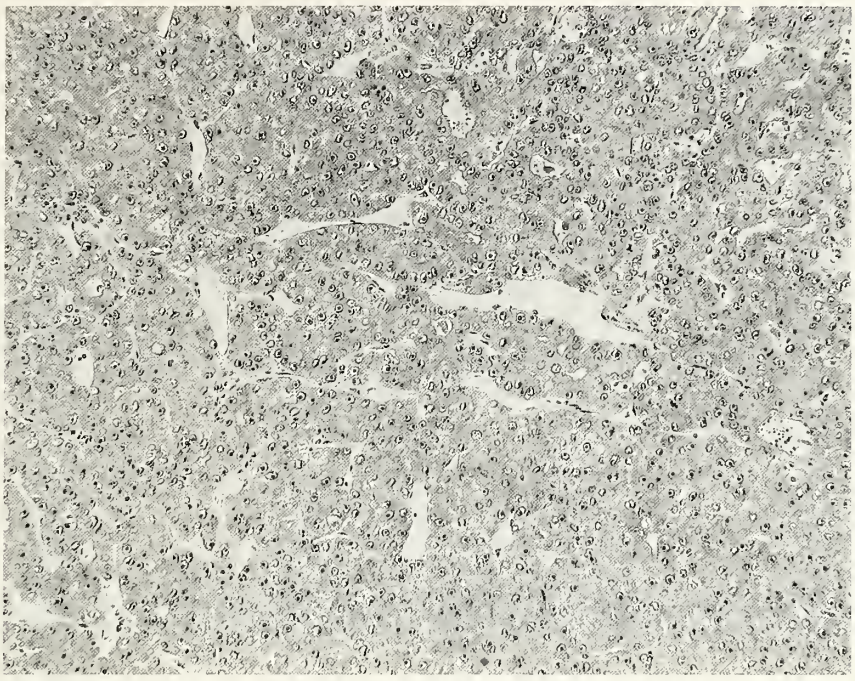


Figure 197
HEPATOCELLULAR CARCINOMA
This grade II hepatocellular carcinoma has hepatocellular origin readily recognizable by polygonal cells in a trabecular pattern with canaliculi and an endothelial layer that can be identified around the trabeculae. X117.

Alcoholic hyalin (Mallory bodies) were readily found in 4 percent of our hepatocellular carcinoma series. Norkin and Campagna-Pinto reported 20 percent of the cases to have alcoholic hyalin, whereas Nakanuma and colleagues reported Mallory bodies in paraplastic hepatocytes (fig. 200). Pale bodies, as well as hyaline bodies, are noted in hepatocellular carcinoma (fig. 201). Some hyaline bodies stain for α-1-antitrypsin (Alvarez-Sala et al.), although the serum phenotype of such patients is normal MM in most cases (Govindarajan et al.). The pale bodies are not Shikata positive, nor are they related to HBV. Fibrinogen has been identified in some pale bodies (Stromeyer et al.). Nuclear inclusions may be cytoplasmic invagination. Fatty change may occur within the tumor cell cytoplasm, even though the nontumor liver shows no significant fatty change (figs. 202-204).

Calcification in hepatocellular carcinoma may occur due to tumor necrosis and degeneration or ossification. Dystrophic calcification is rare, but may be extensive and may be detected by radiographic examination (Chin et al.). An unusual example of calcification in which the tumor had trabecular hepatocellular carcinoma, transition to a small cell anaplastic carcinoma, and a small cell hepatocellular carcinoma with ossification was reported by Maeda and associates (fig. 205).

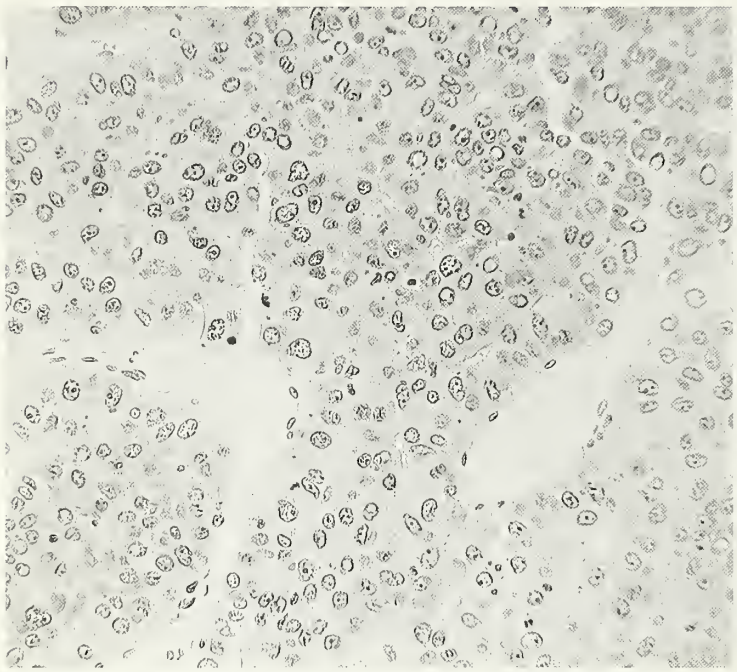


Figure 198
(Figures 198, 190, and 201
are from the same patient)
HEPATOCELLULAR CARCINOMA
The trabecular hepatocellular carcinoma has trabeculae covered by a thin rim of endothelial cells. X235.

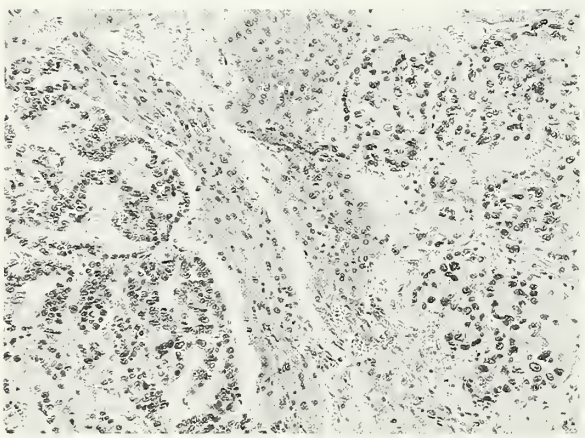


Figure 199
HEPATOCELLULAR CARCINOMA
Focal papillary change is present in this hepatocellular carcinoma with adjacent trabecular hepatocellular carcinoma. X70. (Courtesy of Dr. William Graham, East Liverpool, Ohio.)

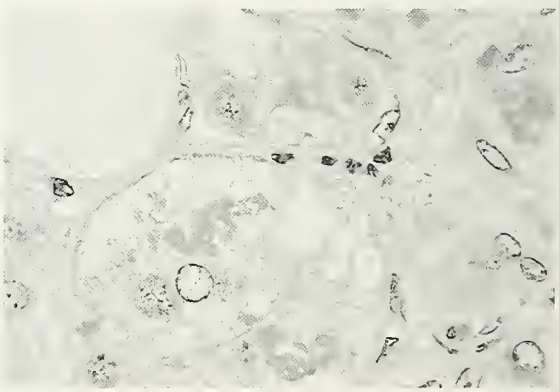


Figure 200
(Figures 200 and 177 are from the same patient)
HEPATOCELLULAR CARCINOMA
Abundant alcoholic hyalin within malignant hepatocytes are seen in the small hepatocellular carcinoma in figure 177. The cellular changes resemble alcoholic hyalin within benign hepatocytes, but no alcoholic hyalin was noted in the adjacent nontumor liver. (Courtesy of Drs. Lillian Rowan and Robert Rosser, Burbank, California.)

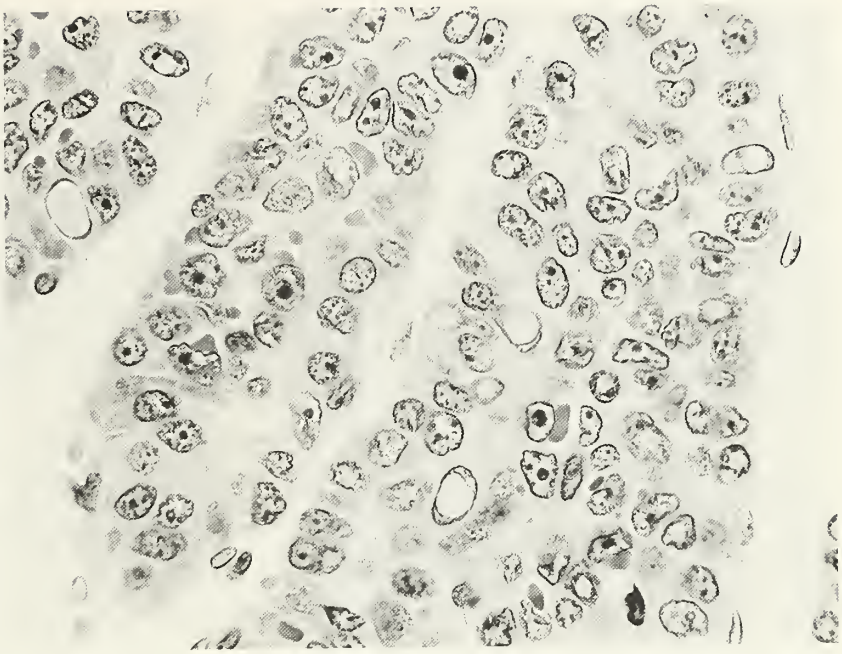


Figure 201
(Figures 201, 190, and 198 are from the same patient)
HEPATOCELLULAR CARCINOMA
There are numerous cytoplasmic pale bodies and small hyaline bodies in this grade III trabecular hepatocellular carcinoma. X585.

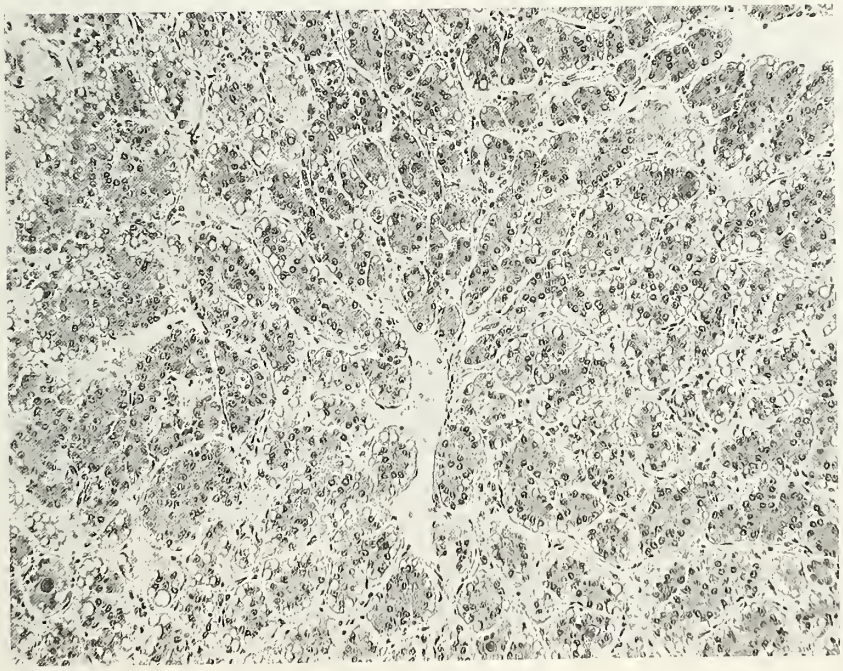


Figure 202
(Figures 202 and 180 are from the same patient)
HEPATOCELLULAR CARCINOMA
This trabecular hepatocellular carcinoma has foamy, fatty change occupying half the cytoplasm. This fatty change is unusual in our material. X117.

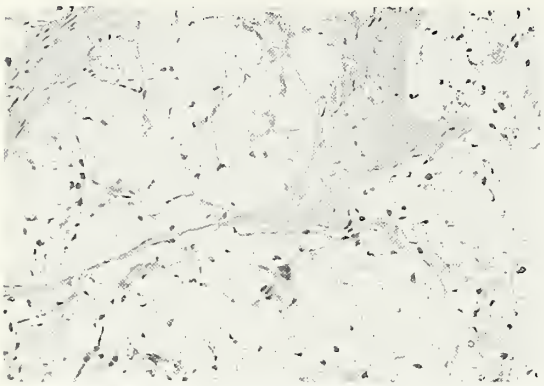


Figure 203
(Figures 203 and 204 are from the same patient)
HEPATOCELLULAR CARCINOMA
Marked fatty change in this hepatocellular carcinoma makes recognition of carcinoma difficult. At low magnification, the wide expanse of fatty change without portal areas indicates neoplastic growth. Examination of numerous sections for typical trabecular hepatocellular carcinoma is recommended. X420.

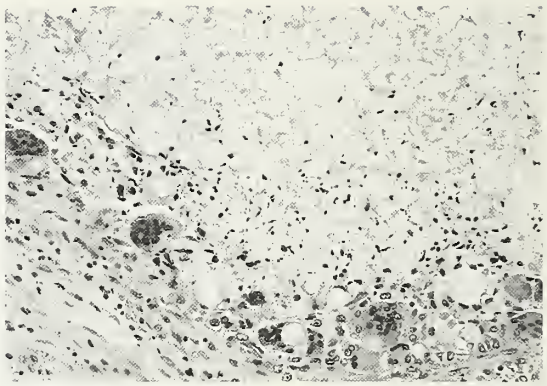


Figure 204
HEPATOCELLULAR CARCINOMA
The marked fatty change in this hepatocellular carcinoma has multinucleated giant cells and appears to be a reaction to the fat breakdown. X420.

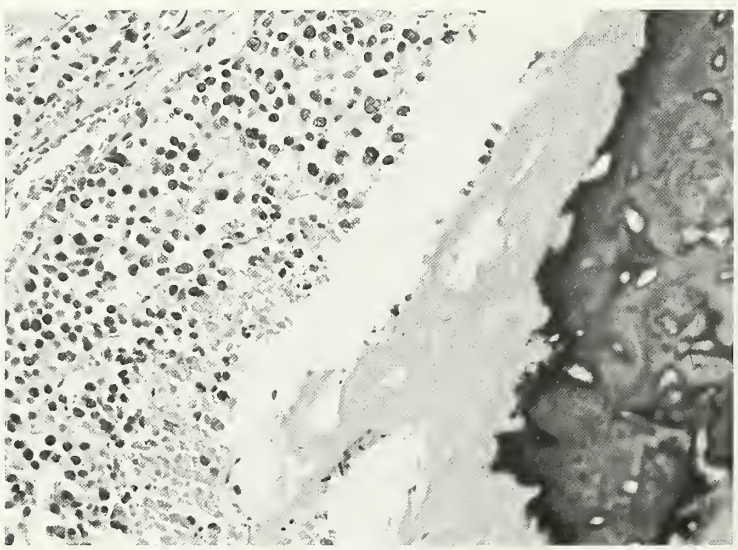


Figure 205
HEPATOCELLULAR CARCINOMA
Ossification and calcification within a grade IV hepatocellular carcinoma required numerous sections to find areas recognizable as hepatocellular carcinoma. X620. (Courtesy of Dr. Masato Maeda, Yokosukashi, Japan.)

Electron microscopy may be useful in distinguishing hepatocellular carcinoma from metastatic carcinoma and cholangiocarcinoma (Ordonez and Mackay). Although the ultrastructural features of hepatocellular carcinoma are variable, the cytoplasmic organelles resemble normal hepatocytes and atypical inclusions are noted. Usually, the histologic grade is related to the amount and type of cytoplasmic organelles. Well-differentiated hepatocellular carcinomas have features of normal hepatocytes, whereas moderately differentiated hepatocellular carcinomas have nuclear invagination and loss of cytoplasmic organization with variable numbers of mitochondria that often contain mitochondrial inclusions. The rough endoplasmic reticulum may be increased or distended, and the smooth endoplasmic reticulum often forms a whorled pattern called "fingerprinting" or "myelin" figures (Ordonez and Mackay; Schaff et al.). Electron-dense bodies may be numerous and appear to correspond to α-1-antitrypsin (by immunohistochemical staining). Bile canaliculi are present, but are diminished in number. The primary role of electron microscopy may be to identify metastatic tumor by recognizing specific features such as secretory granules, melanin pigment, and zymogen granules (Ordonez and Mackay).

Variants of Gross Growth Patterns. Several categories of hepatocellular carcinoma variants are useful in clinical and pathologic classification. Many of these variants are based on histologic features and are discussed as separate topics, but others are: (1) small (or minute) hepatocellular carcinoma; (2) pedunculated hepatocellular carcinoma; and (3) intrabiliary hepatocellular carcinoma.

The definition of small hepatocellular carcinoma has changed as the minimum size of reliable detection decreases due to better technics. Several investigations of small hepatocellular carcinoma are available and the size criteria diminished from 4.5 and 3.5 to 2 cm in diameter (Japan Liver Cancer Study Group; Kondo et al.; Okuda et al., 1977b). A review of 61 resected small hepatocellular carcinomas (less than 3 cm in diameter) by Kanai and associates resulted in a revised classification of the growth pattern into five categories, of which an improved survival rate was associated with the single nodular type (type 1). Early hepatocellular carcinoma, less than 1.2 cm in diameter, appears as a tiny, yellow-green nodule with the adjacent portal areas and bile ducts intact, not compressed by expansile growth. Within the small hepatocellular carcinoma nodule, trabecular or acinar formation is present, which allows diagnosis of carcinoma.

Pedunculated hepatocellular carcinoma is unusual, but amenable to surgical resection (Moritz et al.). Angiography and CT scan have been diagnostic in several patients (Horie et al.). These tumors may appear to be extrahepatic and may arise from accessory lobe or ectopic hepatic tissue. The histologic features are variable, comparable to the variety noted in any large series. We have one example of the fibrolamellar hepatocellular carcinoma occurring in mesentery that is probably extrahepatic tissue with tumor development. A pedunculated fibrolamellar hepatocellular carcinoma has previously been reported (Afroudakis et al.).

Intrabiliary hepatocellular carcinoma may present with striking jaundice and fluctuating jaundice during the course of

disease (Afroudakis et al.; Carella et al.; Kojiro et al., 1982). Intrabiliary tumor growth beyond the hilum was noted in 12 of 232 hepatocellular carcinomas in the Kurume University autopsy series and four patients had obstructive jaundice as the presenting sign (Nakashima et al., 1983). This form is more common in cirrhotic liver, has a slightly shorter survival as a group, and occasionally (21 percent) demonstrates hemobilia (Kojiro et al., 1982). Biliary tract invasion is less frequent than portal vein or hepatic vein invasion (2 versus 54 percent, and 19 percent in the Carella series). Also, invasion of the biliary tree by metastatic tumor is less common and cholangiocarcinoma is a more frequent cause of intrahepatic jaundice by a primary hepatic malignant tumor.

Variants of Histologic Growth. Important or unusual histologic variants include: (1) borderline hepatocellular carcinoma (pure grade I); (2) pigmented hepatocellular carcinoma; (3) fatty hepatocellular carcinoma; and (4) hepatocellular carcinoma with duct transformation. Borderline hepatocellular carcinoma, also called "adenomatous" hepatocellular carcinoma, resembles a benign hepatocellular adenoma by histologic and gross examination. The tumor is the expanding type and not entirely homogenous on cut surface. These tend to occur in the normal liver and the histologic features are very bland hepatocellular carcinoma without dysplasia. The hepatocytes are arranged in cords only two or three cells in thickness. Metastases prove the malignant capacity. In the absence of oral contraceptive use, hepatocellular adenomas with unusual growth pattern, such as acinar formation, are best considered borderline hepatocellular carcinomas (grade I). Pigmented hepatocellular carcinoma is rare and occurs in the normal liver (pl. VIII-D). The cut surface is charcoal gray. Hemorrhage and necrosis may be present and the microscopic growth pattern of several tumors has been microtrabecular and compact hepatocellular carcinoma with dark brown intracytoplasmic pigment resembling Dubin-Johnson pigment (fig. 183). Electron microscopy demonstrated that the pigment was within electron-dense bodies (Roth et al.).

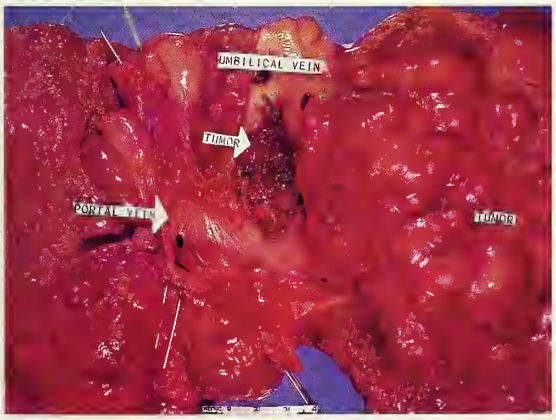
Fatty hepatocellular carcinoma may have a bland histologic appearance; however, with multiple sections, the typical trabecular hepatocellular carcinoma is usually found (figs. 202-205). The cytoplasm is clear, but the rounded cytoplasmic borders with the nucleus eccentrically located indicate the central vacuolated area is fat and not glycogen of the clear cell hepatocellular carcinoma. No unusual clinical pattern is known for this type, which may constitute small areas of many hepatocellular carcinomas.

Ductal transformation of hepatocellular carcinoma occurs in 5 to 10 percent of hepatocellular carcinomas. Although it may be only a small part of the whole tumor, some tumors, especially those arising in a cirrhotic liver, may be entirely this type (fig. 206). Such variation arises in the more densely fibrotic liver, which seems to induce the trabeculae to transform into neoplastic ducts (figs. 207, 208). Transition forms of hepatocellular carcinoma to ductal change are common and some areas are cuboidal cells with small nuclei lacking nucleoli. Some ductal structures contain bile in the lumen. If there is extreme fibrosis and small ductular areas with eosinophilic cuboidal epithelium, we apply the term sclerosing hepatic

PLATE VIII
HEPATOCELLULAR CARCINOMA

A. This encapsulated hepatocellular carcinoma arose in B viral cirrhosis of a Mexican man. The growth pattern within the encapsulated portion is nodular and similar to the cirrhotic liver. There has been spread of the hepatocellular carcinoma outside the encapsulated mass.

B. The cut surface of a minute hepatocellular carcinoma has bile staining and is slightly softer than surrounding cirrhosis.



C. This hepatocellular carcinoma has invaded the intrahepatic portal veins and extended to the umbilical vein of the left lobe.

D. A heavily pigmented pseudoadenomatous hepatocellular carcinoma arose in a young woman not on birth control pills. There is some variation in the degree of pigmentation which by light microscopy is Dubin-Johnson-like pigment. (Courtesy of Dr. Robert M. Cardelli, Santa Clara, California.)

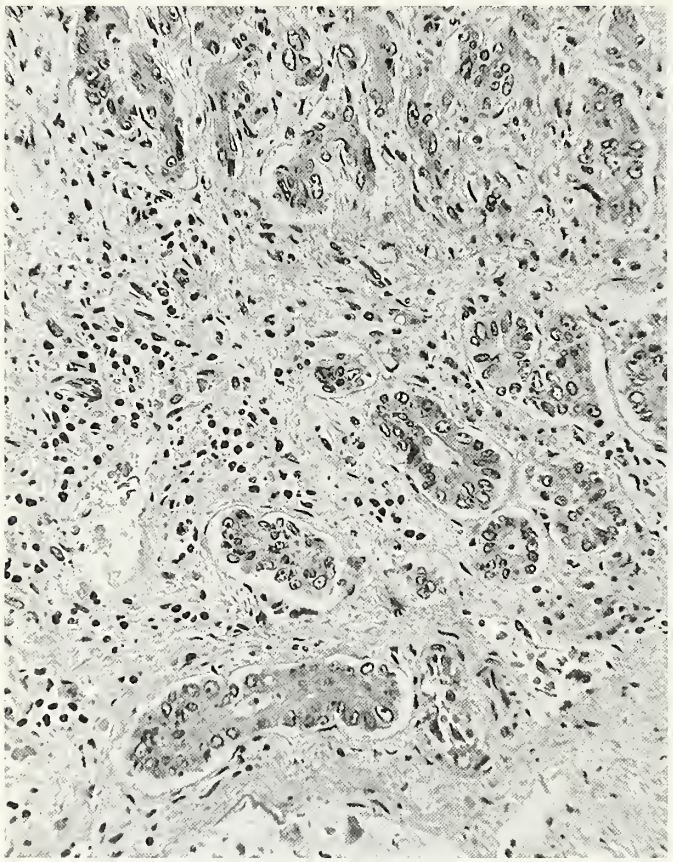


Figure 206
HEPATOCELLULAR CARCINOMA
A duct-like hepatocellular carcinoma has deep eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli that reflect the hepatocellular origin. X235.

carcinoma. Children with biliary atresia have been reported to have hepatocellular carcinoma with duct-like features (Kulkarni and Beatty). Unlike ductal transformation of hepatocellular carcinoma, the combined hepatocellular carcinoma has large areas of both typical hepatocellular carcinoma (usually trabecular type) and a cholangiolar cacinoma. (See Combined Hepatocellular Carcinoma.)

Differential Diagnosis. The histologic diagnosis of hepatocellular carcinoma is highly variable in difficulty, depending upon the quality and amount of the specimen and the differentiation of the tumor. The major challenge is to separate metastatic carcinoma from hepatocellular carcinoma and several variants described in later sections make recognition more difficult than the typical trabecular hepatocellular carcinoma. However, grade IV hepatocellular carcinoma may resemble metastatic adenocarcinoma from the stomach, pancreas, and lung. Important features favoring hepatocellular carcinoma are: the presence of bile production; sinusoidal lining sheath around the tumor cell cluster; absence of sinusoidal infiltration; eosinophilic cytoplasm; prominent nucleoli; portal vein invasion; traceability to

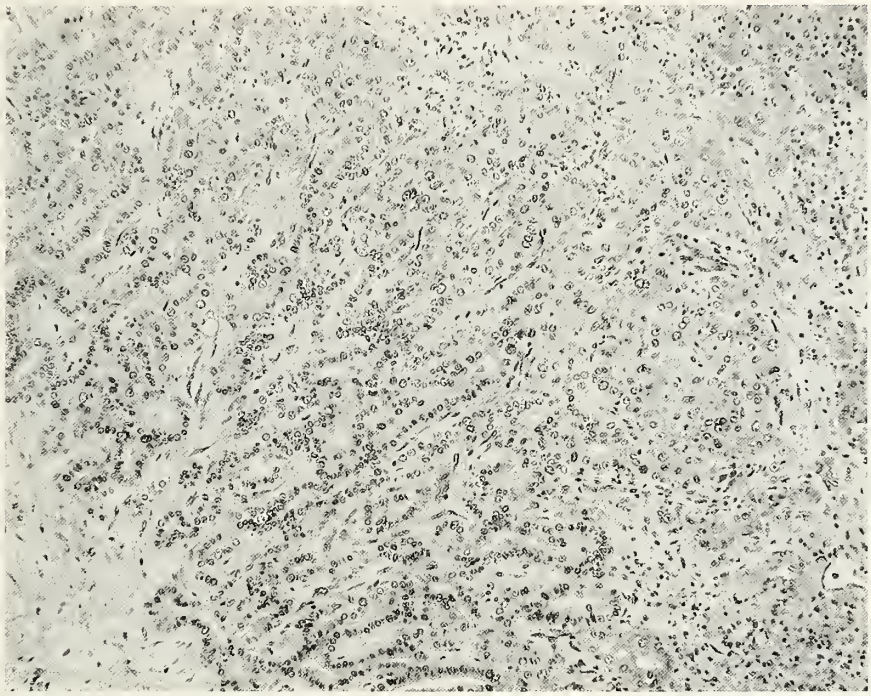


Figure 207
HEPATOCELLULAR CARCINOMA
This hepatocellular carcinoma has transition of trabecular growth to duct-like growth pattern with moderately dilated acini that are elongated openings. X117. (Courtesy of Dr. J.B. Horrell, Castro Valley, California.)

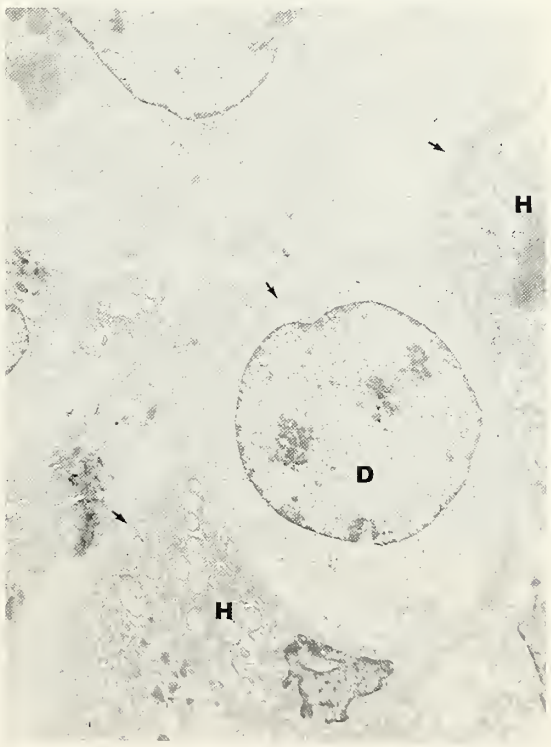


Figure 208
HEPATOCELLULAR CARCINOMA
This electron micrograph reflects the mixture of ductal (D) and hepatocellular (H) features in this hepatocellular carcinoma. The duct-like cells are smaller than hepatocytes, have less cytoplasm, contain little rough endoplasmic reticulum, no glycogen, and have smaller, fewer mitochondria. X10,540.

trabecular hepatocellular carcinoma; and alcoholic hyalin (figs. 196, 209-216). Other features, such as giant cell change and spindle cell formation, are not common in hepatocellular carcinoma.

Metastatic carcinoid tumor, melanoma, and squamous carcinoma may be difficult to distinguish from hepatocellular carcinoma. Carcinoid tumors often grow in pseudotrabecular fashion; so-called pseudotrabecular because there is little endothelial sheath present, although the epithelial cells may be arranged in packets or nests like trabeculae. Also, individual epithelial cells have bland nuclei without nucleoli, in contrast to hepatocellular carcinoma. Some carcinoid tumors (or islet cell tumors) also have some sclerosis between nests which may mimic cholangiocarcinoma. The presence of nucleoli is a hallmark of metastatic melanoma and the growth in pseudotrabeculae may occur. The interface of tumor and normal liver may be helpful as melanoma infiltrates the sinusoids directly on top of endothelial cells. As hepatocellular carcinoma infiltrates the sinusoids, the tumor cells usually interdigitate beneath the endothelial cells. Metastatic squamous carcinoma (from the esophagus, cervix, and gallbladder) may be difficult to distinguish because some macrotrabecular forms of hepatocellular carcinomas have larger tumor cell groupings with prominent cell

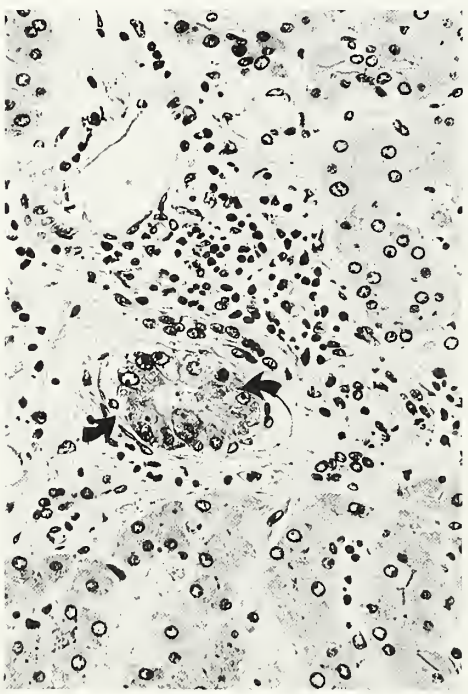


Figure 209
(Figures 209 and 211-214
are from the same patient)
HEPATOCELLULAR CARCINOMA
The portal vein branches are remote from the main tumor and are filled with hepatocellular carcinoma. X235.

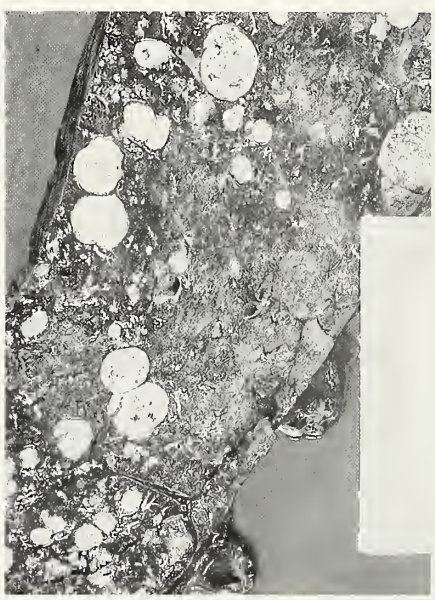


Figure 210
HEPATOCELLULAR CARCINOMA
Embolic metastases to the lung of this hepatocellular carcinoma have enlarged. The fine yellow strand filaments are tumor emboli in smaller vessels.

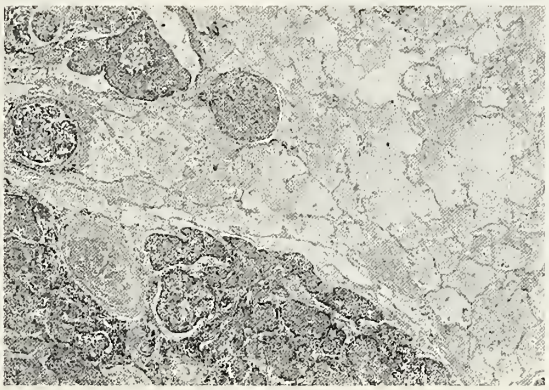


Figure 211
(Figures 211-214 and 209 are from the same patient)
HEPATOCELLULAR CARCINOMA
Metastatic hepatocellular carcinoma forms large clumps of eosinophilic cells within the alveoli and vessels of the lung. X85.

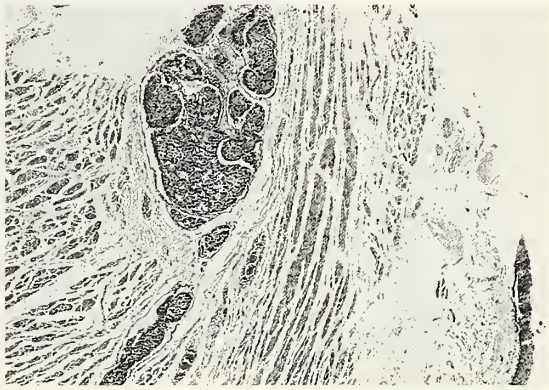


Figure 212
HEPATOCELLULAR CARCINOMA
Large plugs of hepatocellular carcinoma fill the veins within the smooth muscle of the esophagus and are not within the variceal vessels of the submucosa. X85.

Figure 213
HEPATOCELLULAR CARCINOMA
These large polypoid masses of metastatic hepatocellular carcinoma grew on the tricuspid valve. X210.

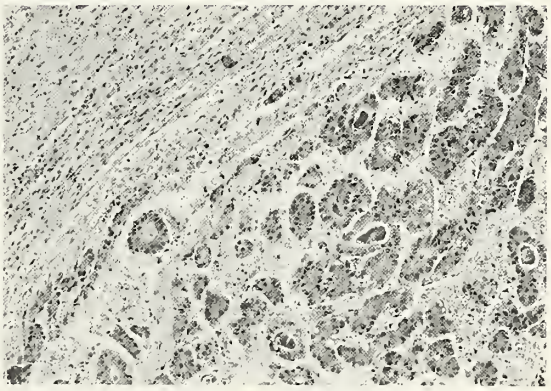


Figure 214
HEPATOCELLULAR CARCINOMA
Large masses of metastatic hepatocellular carcinoma are noted in the adrenal cortex. Bile production is present within the acini. X210.

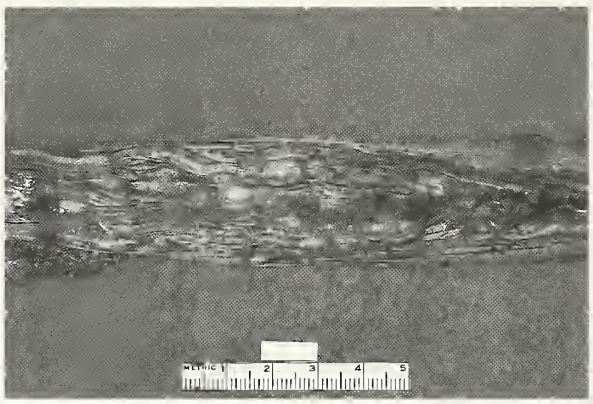


Figure 215
HEPATOCELLULAR CARCINOMA

A 59 year old man with hepatocellular carcinoma developing in a normal liver was admitted for progressive weakness of the lower extremities. This figure shows that the spinal cord has multiple tumor foci in the terminal filaments. There were metastases to the cerebellum and right optic nerve.

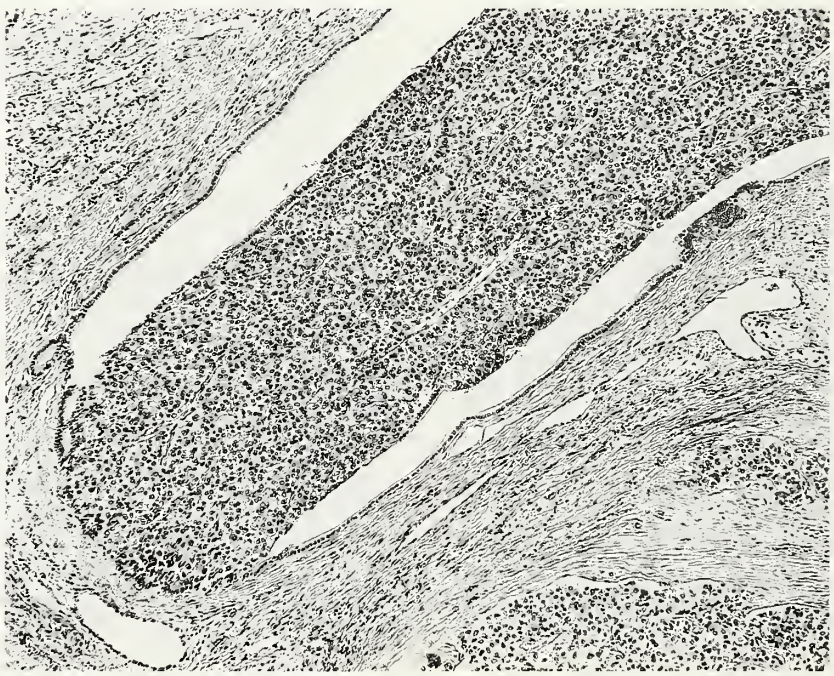


Figure 216
HEPATOCELLULAR CARCINOMA

This hepatocellular carcinoma has attached to an intrahepatic bile duct and forms a polypoid mass within the lumen. X70. (Courtesy of Dr. Jules Kernen, Los Angeles, California.)

membranes, pink or eosinophilic cytoplasm, and may not always have readily identifiable endothelial lining cell on the trabeculae. However, in metastatic carcinoma, a fibrous and inflammatory reaction often accompanies the tumor growth, whereas in hepatocellular carcinoma metastatic to other lobules within the liver, little stromal reaction may occur.

The use of special stains may be helpful. Mucin is rarely seen in hepatocellular carcinoma (adenoid type), as well as adenocarcinoma from other sources. The presence of Fontana-positive pigment is typical of melanoma. Immunochemical stains may be useful. Alpha-fetoprotein immunostaining has been noted in 35 to 73 percent of hepatocellular carcinomas in different laboratories (Kojiro et al., 1981; Thung et al.). The number of positively staining cells and the intensity of staining generally reflect the elevation of serum α-fetoprotein. However, α-fetoprotein staining is relatively insensitive and is noted in only 50 percent of hepatocellular carcinoma (Goodman et al.). Caution is necessary in the interpretation of such stains. Other immunochemical stains may be positive in hepatocellular carcinoma, such as α-1-antitrypsin, albumin, and carcinoembryonic antigen, but whether these reactions can be considered diagnostic of primary tumor rather than metastatic tumor is not certain. Goodman and associates reported a positive reaction for α-1-antitrypsin, fibrinogen, IGG, and carcinoembryonic antigen in both hepatocellular carcinoma and cholangiocarcinoma. Stains for special functions, such as chromogranin, may separate neuroendocrine carcinoma from hepatocellular carcinoma, but difficulties in the interpretation exist when the typical histologic features are trabecular hepatocellular carcinoma, yet the chromogranin reaction is positive.

Prognosis. The prognosis of hepatocellular carcinoma is generally poor unless surgical resection of small tumors is achieved. The more favorable prognostic factors include young age, absence of cirrhosis, small tumor, and complete surgical resection. In the combined hospital survey in Los Angeles, an age below 45 years was associated with mean survival of 40 weeks, versus 9 weeks in the older group (Chlebowski et al.). The influence of cirrhosis is illustrated in the large Japanese series (1978-1979) in which the 50 percent survival time of patients undergoing surgical resection with cirrhosis was 10 months, compared to 20 months without cirrhosis (Liver Cancer Study Group of Japan, 1984). In that series, 50 percent of the patients had laparotomy and 25 percent had resection. Far fewer patients have surgical resection in the United States.

Approximately one-half of the patients with hepatocellular carcinoma have metastasis at autopsy, which is less than the 75 to 80 percent rate of metastasis for cholangiocarcinoma (Table 11). The lungs are a common site of metastasis (figs. 210, 211). Within the liver, the portal vein and major bile ducts may serve to disseminate the tumor (figs. 209, 216). Spread to other sites may be solitary or part of a widespread metastasis. Hepatocellular carcinoma may be identified in the muscle of the esophagus (fig. 212), heart valve (fig. 213), adrenal cortex (fig. 214), spinal cord (fig. 215), and occasionally anywhere in the body.

Table 11

COMPARISON OF METASTATIC PATTERNS OF SCLEROSING HEPATIC CARCINOMA, HEPATOCELLULAR CARCINOMA, AND CHOLANGIOCARCINOMA*

	Percent of Sclerosing Carcinoma (30 cases)	Percent of Hepatocellular Carcinoma, Cirrhotic (188 cases)	Percent of Peripheral Cholangiocarcinoma (18 cases)
No Metastases	20	55	25
Lung	30	39	25
Lymph node (porta hepatis)	30	17	69
Serosa	27	7	25
Portal vein	17	37	12
Hepatic vein	13	23	18
Adrenal gland	13	7	18
Gallbladder	7	5	0
Bone	13	8	25
Spleen	3	2	6
Pancreas	0	1	0
Kidney	0	0	0

* Modification of table 5 from Omata, M., Peters, R.L., and Tatter, D. Sclerosing hepatic carcinoma: relationship to hypercalcemia. Liver 1:33-49, 1981.

DISTINCTIVE HEPATOCELLULAR CARCINOMA VARIANTS

Childhood Hepatocellular Carcinoma

The histologic and gross features of childhood hepatocellular carcinoma are similar to the adult, but the underlying associated conditions are different. Whereas the majority of adult hepatocellular carcinomas arise in chronic liver disease and cirrhosis, only 25 percent of childhood hepatocellular carcinomas do, and many of the remaining hepatocellular carcinomas occur in metabolic disorders.

Incidence. Hepatocellular carcinoma accounted for 20 percent of all primary hepatic tumors treated or seen at The Children's Hospital Medical Center (1924-1981) in Boston, and was the third most common childhood hepatic tumor following hepatoblastoma and vascular tumors (Lack et al., 1983).

Clinical. Underlying hepatic disorders related to hepatocellular carcinoma in childhood include biliary atresia (Okuyama), familial cholestasis (Dahms), glycogen storage disease type I, hereditary tyrosinemia (Weinberg et al.), hyperalimentation, and hepatitis B virus (Wu et al., 1987).

Fibrolamellar hepatocellular carcinoma occurred in seven patients under 21 years of age in the series of 23 we reported (Craig et al.). The average age at diagnosis was 9.7 years and there was a slight male predominance in the Boston hospital survey (Lack et al., 1983).

Pathology. The gross features of childhood hepatocellular carcinoma are related to the underlying associated factors. Although most hepatocellular carcinomas arise in a noncirrhotic liver, at the time of diagnosis the tumor is multifocal and bilateral in the majority of patients (figs. 217, 218). The microscopic features usually show a moderately differentiated hepatocellular carcinoma (figs. 219, 220), and in the case of glycogen storage disease, transition of hepatocellular adenoma to carcinoma is common (fig. 221).

Differential Diagnosis. The metastatic tumors in childhood that resemble hepatocellular carcinoma are similar to those in adults.

Fibrolamellar Hepatocellular Carcinoma

SYNONYMS AND RELATED TERMS: Eosinophilic hepatocellular carcinoma with lamellar fibrosis; hepatocellular carcinoma polygonal cell type with fibrous stroma; fibrolamellar oncocytic hepatoma; oncocytic hepatocellular tumor.

Definition. Fibrolamellar hepatocellular carcinoma is a slowly growing, expanding tumor with septate fibrosis arising in normal liver and is characterized by eosinophilic neoplastic hepatocytes separated into cords by lamellar fibrous strands.

Incidence. In our survey of the 462 malignant epithelial tumors from the LACUSC-MC and USC Liver Unit autopsy series, fibrolamellar hepatocellular carcinoma was recorded five times (1 percent). However, in the 1974 liver tumor survey by Foster and Berman, 125 primary hepatic carcinomas were identified in adults and children and 12 were fibrolamellar hepatocellular carcinoma (10 percent). A survey by Farhi and associates of adults less than

Figure 217
CHILDHOOD HEPATOCELLULAR CARCINOMA
The left lobe of a cirrhotic liver from a 10 year old black male was replaced by hepatocellular carcinoma. Immunoperoxidase stain, performed 15 years after autopsy, established the etiologic association with hepatitis B virus.

Figure 218
(Figures 218 and 219 are from the same patient)
CHILDHOOD HEPATOCELLULAR CARCINOMA
A 3 month old female had biliary atresia and had a Kasai procedure at age 2 months. At autopsy, hepatocellular carcinoma involved most of the liver. (Courtesy of Dr. Robert Hutter, Livingston, New Jersey.)

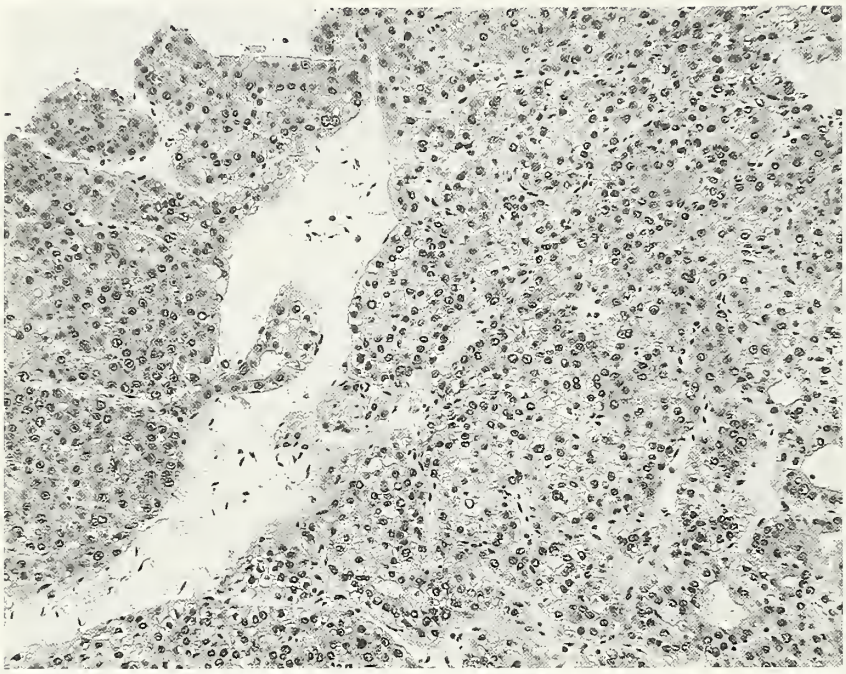


Figure 219
CHILDHOOD
HEPATOCELLULAR
CARCINOMA

A grade II hepatocellular carcinoma with macrotrabecular and compact growth pattern is present in a liver with biliary atresia. X117. (Courtesy of Dr. Robert Hutter, Livingston, New Jersey.)

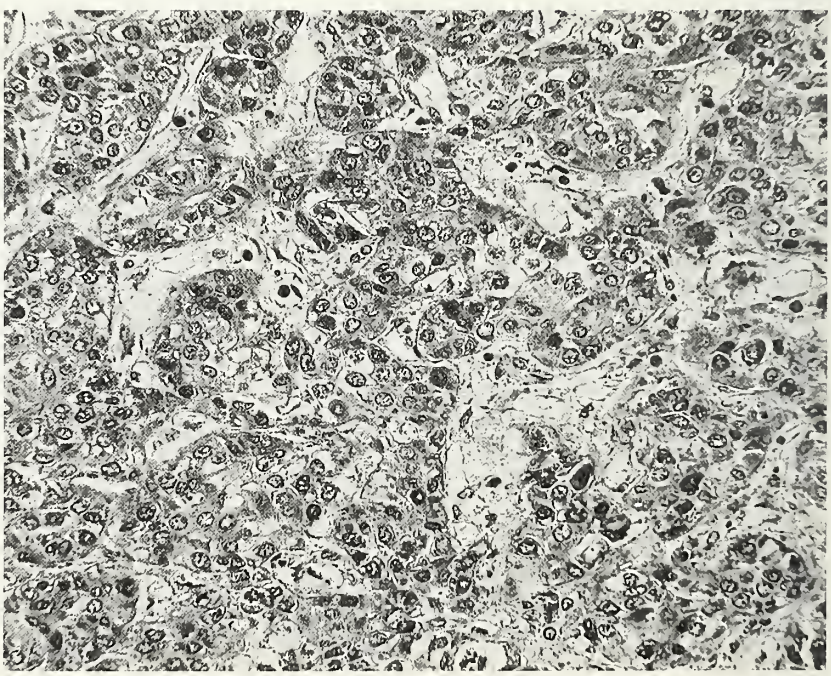


Figure 220
CHILDHOOD
HEPATOCELLULAR
CARCINOMA

The small acini in this hepatocellular carcinoma resemble tubules. The 17 year old male developed progressive cholestasis at 1 year of age. This patient and his twin brother died of hepatocellular carcinoma during their teen years. (Courtesy of Drs. Beverly Dahms and Benjamin Landing, Los Angeles, California.)

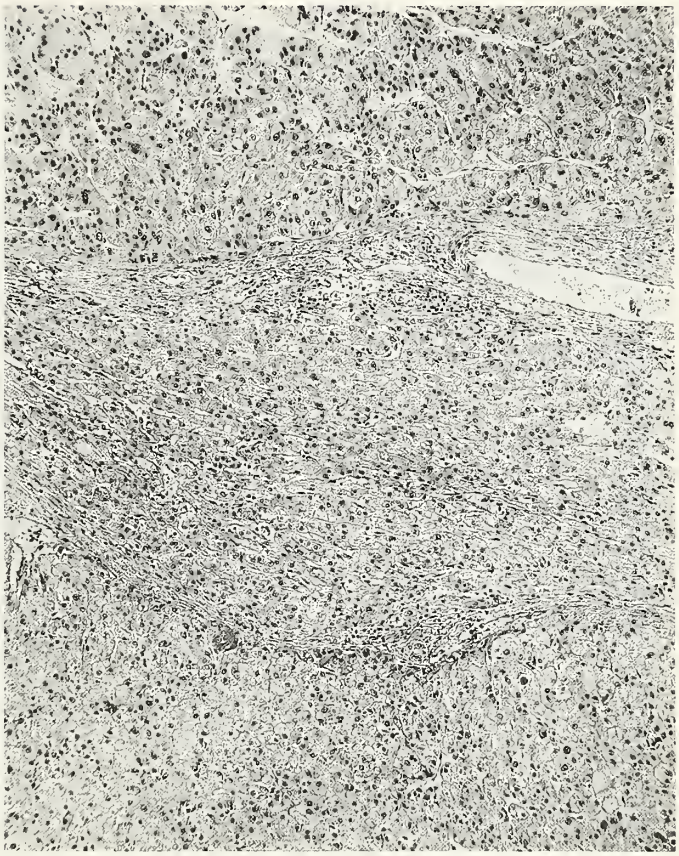


Figure 221
(Figures 221 and 182
are from the same patient)
HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma of the trabecular type (at top of figure) has evolved from a hepatocellular adenoma associated with glycogen storage disease type I in a 29 year old patient. The middle area is normal liver and the bottom is hepatocellular adenoma. The transition is very subtle, and only by reviewing numerous fields can this distinction be appreciated. X117. (Courtesy of Dr. Rodney Howell, Houston, Texas.)

40 years of age revealed that 56 percent of hepatocellular carcinoma were the fibrolamellar hepatocellular carcinoma variant. Therefore, the incidence of fibrolamellar hepatocellular carcinoma depends upon the age of the population and the nature of the survey. This histologic variant has been reported from France, England (Baithun and Pollock), Spain (Caballero et al.), Australia (Cooke et al.), Venezuela (Grases), and Taiwan (Hsu et al.), but is apparently not seen in South Africa (van Tonder et al.) or Malaysia (Sumithran).

Clinical. The young age range of this variant is reflected in all the major surveys. In two separate reports of 35 patients, the average ages were 23.1 years and 26.4 years, and the age range was 5 to 69 years (Berman et al.; Craig et al.). Clinical symptoms are vague and often of long duration, with abdominal pain the most common symptom present many months prior to diagnosis. Laboratory studies indicate the serum α-fetoprotein is rarely elevated; occasionally the serum α-1-antitrypsin is aberrant (MZ phenotype), and in some series the vitamin B_{12} binding protein is elevated (Waxman and Gilbert). Paradinas and colleagues reported that 7 of 10 hepatocellular carcinoma patients with elevated vitamin B_{12} binding had the fibrolamellar hepatocellular carcinoma

variant, but in a large survey of hepatocellular carcinoma patients in South Africa, van Tonder and associates found no fibrolamellar hepatocellular carcinoma in the group, even though 84 percent of the series had mildly elevated levels of the protein. Serum neurotensin levels have been elevated in fibrolamellar carcinomas (Collier et al.).

Radiographic studies often show calcification of the tumor (5 of 13 in the series of Friedman et al.) and ultrasound shows a homogenous mass with central echodensity (Friedman et al.). Angiography studies are similar to focal nodular hyperplasia and arterial embolization has been used to assist resection of a pedunculated fibrolamellar hepatocellular carcinoma (Wong et al.).

Pathogenesis. The etiology of fibrolamellar hepatocellular carcinoma is unknown, but a relationship to environmental agents and drugs has been considered. Edmondson recognized the distinctive histologic features in 1954 (and included them in Fascicle 25 of the First Series) (fig. 222), but more patients were brought to his attention many years later in the 1970s. His observation of more patients in his later and more recent referral series, coupled with the large review of hepatocellular carcinoma in the LACUSC-MC archives dating from 1918 to the present, indicated that the tumor has increased in frequency. The association of hepatocellular adenomas to oral contraceptives is well-established and two young patients in the series by Lack and associates (1983) showed transition of hepatocellular adenoma to hepatocellular carcinoma (not fibrolamellar hepatocellular carcinoma type). However, despite a search of the records, no association of oral contraceptive use and fibrolamellar hepatocellular carcinoma has been noted. Furthermore, the equal sex incidence of fibrolamellar hepatocellular carcinoma indicates that estrogen use alone is not sufficient to account for the tumor.

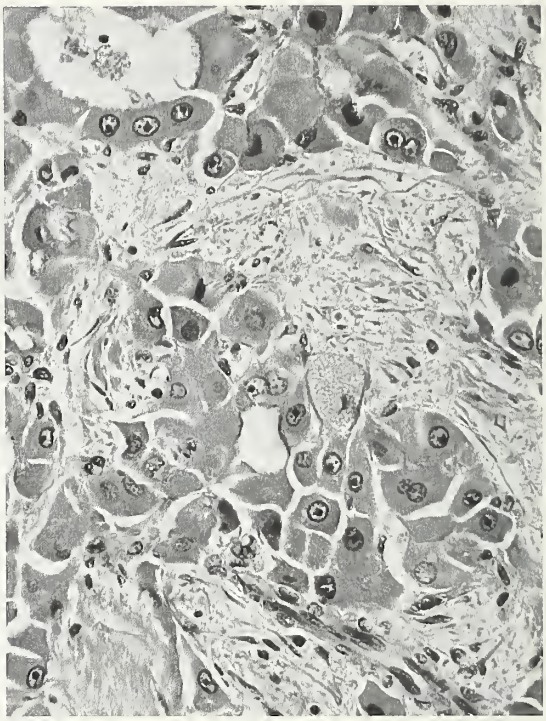


Figure 222
FIBROLAMELLAR HEPATOCELLULAR CARCINOMA
An acinus is noted in the left upper field of this fibrolamellar hepatocellular carcinoma from a 14 year old female. There is moderate variation in nuclear size in these polygonal cells and the cytoplasm is very finely granular (oncocytic). The patient is alive and well 30 years after resection. X295. (Fig. 87 from Fascicle 25, First Series.)

Derivation from focal nodular hyperplasia has been considered because of the gross and microscopic resemblance, and a few fibrolamellar hepatocellular carcinomas also have a separate nodule of focal nodular hyperplasia present in the liver (Vecchio et al.). However, convincing

transition of the focal nodular hyperplasia lesion to fibrolamellar hepatocellular carcinoma has not been demonstrated in any of the 75 patients in our files. Furthermore, the majority of fibrolamellar hepatocellular carcinomas do not have the typical focal nodular hyperplasia gross appearance. The usual carcinoma precursor factors (such as hepatitis B virus, Thorotrast, alcoholic cirrhosis, etc.) do not account for fibrolamellar hepatocellular carcinoma and the fibrolamellar hepatocellular carcinoma variant is rare in areas where hepatocellular carcinoma is high in incidence (i.e., the Far East and Africa). An environmental or drug toxin is a possibility because in the older reviews of hepatocellular carcinoma from the early decades of this century, few or no cases were identified of this variant, suggesting that some new environmental condition or drug may be present. However, no specific agents have been suggested. Moreover, earlier examples may not have been recognized as hepatocellular in origin and thus misclassified.

Gross. Fibrolamellar hepatocellular carcinoma arises in a normal liver in at least 75 percent of the patients and, curiously, the left lobe is more commonly involved than the right (fig. 175) (Craig et al.). Focal nodular hyperplasia (in addition to fibrolamellar hepatocellular carcinoma) was reported in two patients (Berman et al.). Pedunculated lesions occurred in 4 of 17 patients reported by Friedman and colleagues. Chronic liver disease occurs about 20 percent of the time, with cirrhosis in one-half of the patients and fibrosis in the other. In our series, resected specimens were 4 to 17 cm in diameter and weighed up to 3600 g. Necrosis and hemorrhage are noted in the larger specimens, but the usual tumor is bulging, fleshy, brown, and well-demarcated from the adjacent liver. Often a few satellite nodules are present. Two of 23 in our series had typical "focal nodular hyperplasia-type" lesions with a central fibrous scar.

Microscopic. The microscopic pattern is distinctive. The epithelial component consists of eosinophilic cells with granular cytoplasm and prominent nucleoli (figs. 222-225). Glandular structures are not common. Pale bodies (clear areas of cytoplasm) occur in one-half of the cases (fig. 225). Dense bodies also occur in about one-third of the tumors and often are adjacent to the pale bodies. These dense cytoplasmic bodies are PAS positive, but do not stain for α-1-antitrypsin or α-fetoprotein. Extracellular droplets which stain like mucin are noted and stain positively for albumin and α-1-antitrypsin. The presence of a copper binding protein has been observed (Lefkowitch et al.) and occurs in the majority of tumors, unlike typical hepatocellular carcinomas, which usually lack such a marker (Sheahan). Cholestatic plugs are frequently noted in some tumors. The fibrous component often accounts for one-half of the tumor and is composed primarily of thin multilamellated strands of collagenous fibers (figs. 223, 224). In larger tumors, these fibrous areas may be very large central scars and contain only a few residual epithelial cells.

Tumor growth into bile ducts and portal veins is not unusual and a few patients develop jaundice. Furthermore, a pelioid pattern with larger, dilated sinusoids occurs in one-third of the cases. This pelioid pattern is usually a moderate size area (one or several blocks) and does not extend uniformly throughout the tumor. We have four patients diagnosed with

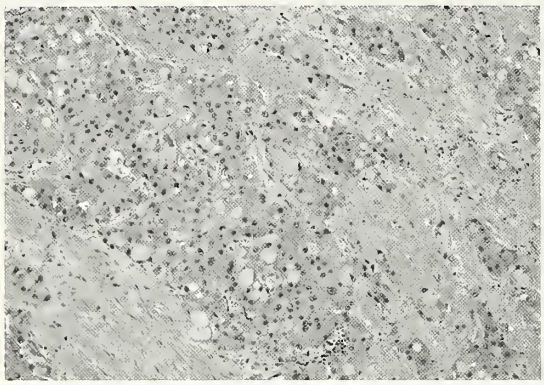


Figure 223
(Figures 223-225 and 176 are from the same patient)
FIBROLAMELLAR HEPATOCELLULAR CARCINOMA
This figure shows a fibrolamellar hepatocellular carcinoma with intermixing of broad fibrous strands and trabeculae of polygonal eosinophilic carcinoma. X210. (Courtesy of Dr. Edward Smith, Jackson, Mississippi.)

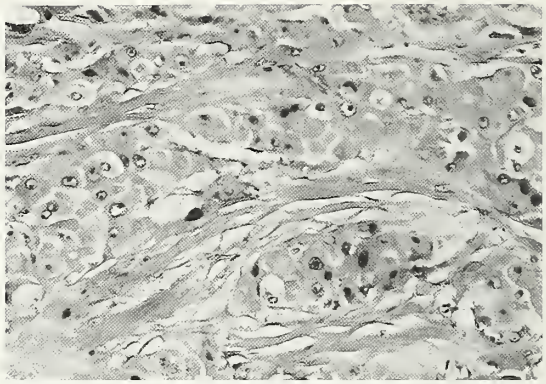


Figure 224
FIBROLAMELLAR HEPATOCELLULAR CARCINOMA
This fibrolamellar hepatocellular carcinoma has thin lamellar fibrous strands that often break apart in routine paraffin embedding technic. The nuclei are round and uniform with small nucleoli (grade II). X420. (Courtesy of Dr. Edward Smith, Jackson, Mississippi.)

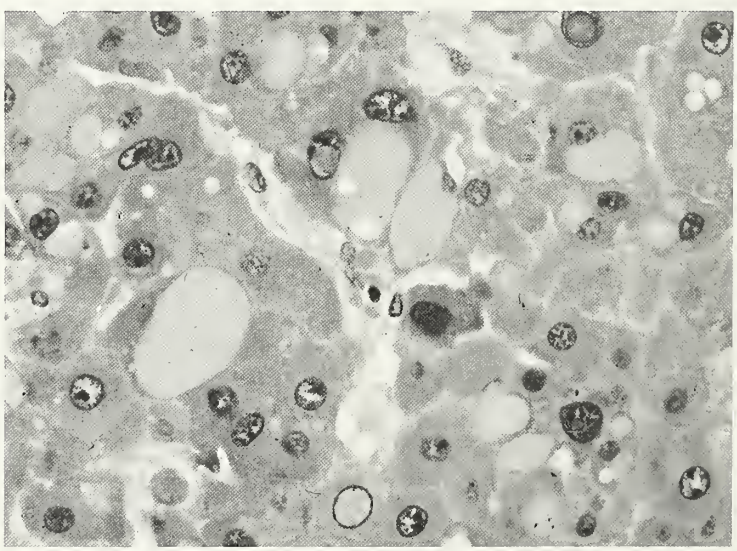


Figure 225
FIBROLAMELLAR HEPATOCELLULAR CARCINOMA
Numerous cytoplasmic pale bodies of variable size are noted in this fibrolamellar hepatocellular carcinoma and in some areas, PAS positive droplets occur within the pale bodies. X1240. (Courtesy of Dr. Edward Smith, Jackson, Mississippi.)

a mixture of fibrolamellar hepatocellular carcinoma pattern and typical trabecular hepatocellular carcinoma.

Electron microscopy of the epithelial component reveals the granular cytoplasm (called oncocytic by some) is due to abundant mitochondria (fig. 226), some of which also contain small granular dense bodies. The increase in mitochondria also is noted in the nontumor of the same patients (Yuhui). The pale bodies are composed of microvilli.

Enzyme histochemistry reflects the abundant mitochondria by having high enzyme activity. Uchida and associates demonstrated that succinic dehydrogenase and glucose-6-phosphatase activity was greater in fibrolamellar hepatocellular carcinoma than in the nontumor epithelial cells of the same patient. Fine needle aspiration may yield the large polygonal eosinophilic cells and fragments may have the lamellar fibrosis. The pale bodies and intracytoplasmic hyaline globules are also helpful clues (Suen et al.).

Differential Diagnosis. Hepatocellular carcinoma, including the sclerosing variant, focal nodular hyperplasia, metastatic carcinoma (especially a sclerosing type), and metastatic endocrine tumors (such as pheochromocytoma) are considered in the differential diagnosis. Fortunately, most fibrolamellar hepatocellular carcinomas are fairly uniform in histologic appearance and a few sections will demonstrate the admixture of thin trabeculae and lamellar fibrosis. However, in 25 percent, areas may be atypical and include either typical trabecular hepatocellular carcinoma or the pelioid change. In addition, many sclerosing hepatocellular carcinomas have a few areas with mixtures of fibrosis (that is not lamellar) with eosinophilic hepatocellular carcinoma cells that mimic fibrolamellar hepatocellular carcinoma. Numerous blocks may be needed to find the lamellar fibrosis required for the diagnosis of fibrolamellar hepatocellular carcinoma. Cholangiocarcinoma also has fibrosis (not lamellar), but the epithelial component is small cuboidal type and not large polygonal eosinophilic cells. Focal nodular hyperplasia does not have cellular atypia as does fibrolamellar hepatocellular carcinoma. Some metastatic endocrine tumors produce sclerosis (not the lamellar type) and the epithelial component usually does not have prominent nucleoli as noted in fibrolamellar hepatocellular carcinoma. One sclerosing squamous carcinoma of the gallbladder invaded the liver and was extremely difficult to exclude in our original series. Several sections were obtained of the gallbladder bed demonstrating the site of origin of the tumor.

Prognosis. Fibrolamellar hepatocellular carcinoma has a better prognosis than typical hepatocellular carcinoma, as observed in several studies (Berman et al.; Craig et al.) and by Edmondson in 1956. The average survival rate of 32 months and high operability (48 percent) distinguish fibrolamellar hepatocellular carcinoma from hepatocellular carcinoma. Farhi and associates reported that long-term survivors occurred only with the fibrolamellar hepatocellular carcinoma variant in the series of 23 young hepatocellular carcinoma patients. Extensive surgical resection and transplantation may be performed successfully '(Starzl et al.). However, clean resection has produced a better survival rate than transplantation. Starzl and associates reported a 50 percent recurrence rate and two deaths due to advanced metastatic disease in six

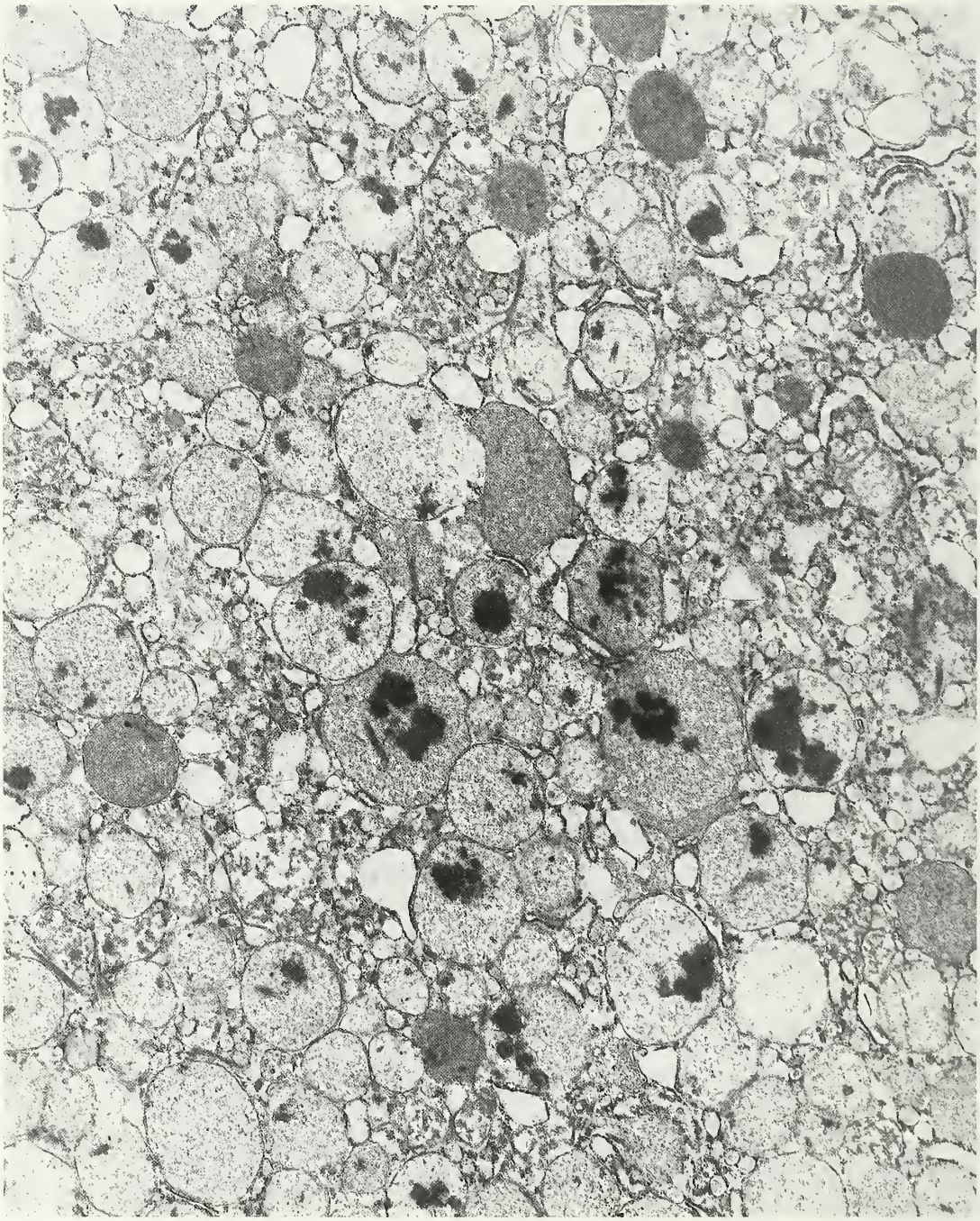


Figure 226
FIBROLAMELLAR HEPATOCELLULAR CARCINOMA
The epithelial cells in this fibrolamellar hepatocellular carcinoma contain abundant mitochondria that have granules and a deficiency of cristae. X4380. (Courtesy of Dr. Xu Yuhui, Wuhan, People's Republic of China.)

patients with orthotopic hepatic transplantation. Selected resection of isolated metastasis has also been beneficial. Radiation therapy and conventional chemotherapy have not been effective.

Spindle Cell Hepatocellular Carcinoma

Spindle cell hepatocellular carcinoma, also called sarcomatoid hepatocellular carcinoma, occurs in approximately 3 to 5 percent of hepatocellular carcinomas and may be only a small area or form a major tumor mass (Kakizoe et al.). In a report of 14 cases, Kakizoe and colleagues found a marked male predominance (12:2), with the age range of 46 to 71 years. Cirrhosis was documented in 64 percent of the cases. The clinical findings were similar to typical hepatocellular carcinoma and are relatively nonspecific. An unusual case in our series occurred in a young woman with bony metastasis as the first detected tumor. The spindle cell neoplasm was carcinoembryonic antigen positive, and thus diagnosed as metastatic carcinoma. Further evaluation demonstrated hepatocellular carcinoma by a needle biopsy of the liver. Subsequent autopsy demonstrated transition of spindle cell hepatocellular carcinoma to trabecular hepatocellular carcinoma (figs. 227, 228). A normal (low) serum α-fetoprotein is more common in this group than in the typical hepatocellular carcinoma.

Pedunculated hepatocellular carcinomas represented an unusually large number (three) in the group of 14 cases (Kakizoe et al.). The tumor size was 5 to 18 cm and necrosis was common. The histologic features in 12 patients showed sarcomatous areas merging with trabecular or pseudoglandular hepatocellular

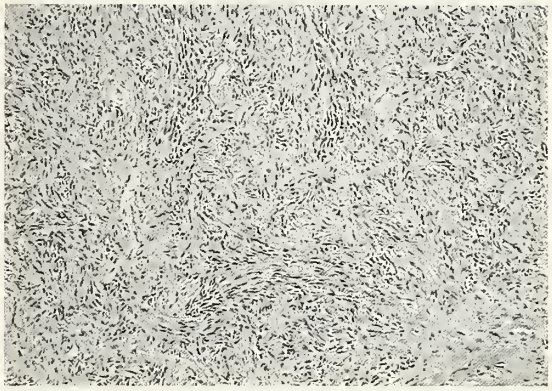


Figure 227
(Figures 227, 228, and 234 are from the same patient)
SPINDLE CELL HEPATOCELLULAR CARCINOMA
This spindle cell hepatocellular carcinoma has interweaving fascicles of relatively bland spindle cells with small nuclei. There are a few scattered elongated thin vascular channels. This component was approximately 40 percent of a combined hepatocellular carcinoma and cholangiocarcinoma in an alcoholic cirrhosis. Transition of all three major histologic patterns was evident and were distinctly different by gross examination. The spindle cell hepatocellular carcinoma was the most firm and appeared as a pale, white, bulging area. X210.

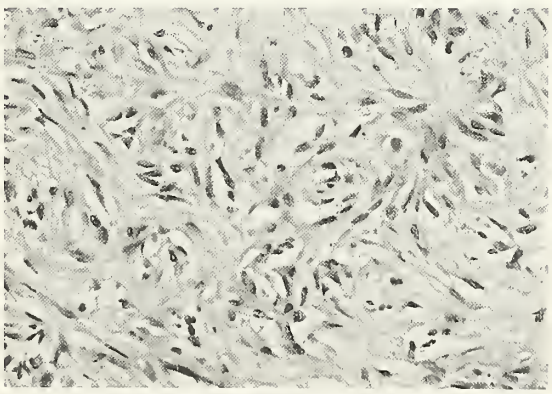


Figure 228
SPINDLE CELL HEPATOCELLULAR CARCINOMA
These spindle cells have indistinct cytoplasmic borders and few mitoses. Other fields had transition to trabecular hepatocellular carcinoma. X840.

carcinoma, whereas two tumors were only sarcomatoid. These sarcomatoid areas resembled leiomyosarcoma, fibrosarcoma, and even malignant fibrous histiocytoma. Some areas in our cases lack pleomorphic features or mitosis and are so bland that a needle biopsy could be considered benign.

Metastasis is more common in spindle cell hepatocellular carcinoma than typical hepatocellular carcinoma and the histologic appearance of the metastasis may be trabecular hepatocellular carcinoma as well as sarcomatoid hepatocellular carcinoma. Immunochemical study showed that vimentin and keratin were stainable in 64 percent of spindle cell hepatocellular carcinomas, yet the control group of typical hepatocellular carcinomas showed vimentin and keratin staining of 5.6 and 84.2 percent, respectively.

Clear Cell Carcinoma

SYNONYMS AND RELATED TERMS: Fat cell hepatocellular carcinoma; fatty hepatocellular carcinoma.

Definition. Clear cell hepatocellular carcinoma applies to the tumor with at least 50 percent of the total volume of tumor cells having clear cytoplasm which, by special staining technics, is either large quantities of glycogen or fat.

Incidence. The incidence of clear cell hepatocellular carcinoma appears to vary considerably around the world. In the Hong Kong series, 25 percent of the hepatocellular carcinomas had 30 percent or more of the total tumor being clear cells, and 12.5 percent had more than 50 percent of the tumor cells of the clear cell type (Wu et al., 1983). In the New York series, 8.7 percent of 150 primary hepatic carcinomas had clear cell areas. A large national U.S. series indicated seven clear cell hepatocellular carcinomas in the group of 112 hepatocellular carcinomas (Foster and Berman). However, many reports include the term clear cell if a major area is clear cell type (less than 50 percent).

Clinical. The majority of patients with clear cell hepatocellular carcinomas have the clear cellular change in only part of the neoplasm and usually have no unusual clinical features (Buchanan and Huvos). However, hypoglycemia with or without hypercholesterolemia has been reported (Anthony; Sasaki et al.). More often, hypoglycemia in hepatocellular carcinoma patients is not associated with clear cell change, but occurs with either terminal hepatic failure from massive tumor replacement or for no apparent reason in typical trabecular hepatocellular carcinoma.

Pathology. Two of six patients had cirrhosis in the series of Foster and Berman and most series report a lower occurrence of clear cell hepatocellular carcinoma in cirrhosis than in noncirrhosis. Also, the usual clear cell hepatocellular carcinoma is a large solitary mass but may have satellite nodules. The cut surface of the nodules may be yellow due to the lipids within the cells (Sasaki et al.).

The microscopic features are variable; most cases have large areas of typical hepatocellular carcinoma including trabecular, acinar, anaplastic, and desmoplastic patterns (Buchanan and Huvos). Often the clear cell change merges into and is part of the trabecular pattern, with the eosinophilic cells having transition forms to clear cell areas. The clear cells have abundant cytoplasm that stains positively for glycogen or fat and the nuclei are usually small (figs. 201-203, 229, 230). The cells form large masses without sinusoidal lining cells or

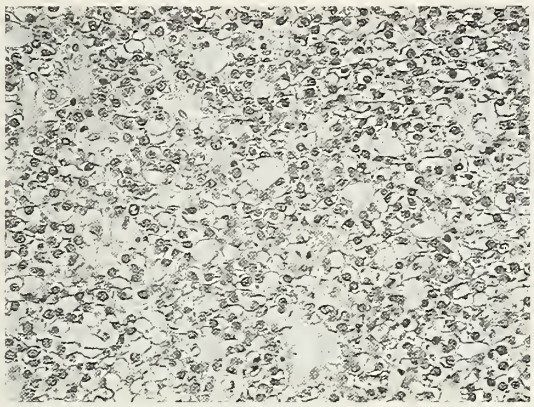


Figure 229
(Figures 229 and 230 are from the same patient)
CLEAR CELL CARCINOMA
This clear cell hepatocellular carcinoma has small round nuclei with abundant clear cytoplasm that is PAS positive before diastase. A suggestion of a trabecular pattern remains. X200.

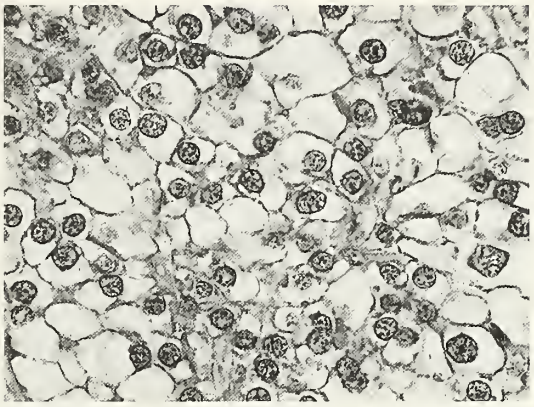


Figure 230
CLEAR CELL CARCINOMA
Round nuclei without nucleoli and abundant cytoplasm are features of metastatic clear cell carcinoma from the thyroid or kidney as well as this clear cell hepatocellular carcinoma. X550.

cord growth pattern. Metastatic hepatic tumor also has clear cell changes and multiple sections of the primary tumor may be necessary to verify the hepatocellular origin of the metastasis. In selected areas, the clear cell tumor may mimic clear cell carcinoma of the kidney with small nuclei lacking both nucleoli and a conventional hepatocellular carcinoma trabecular pattern. A small biopsy from such a tumor is easily mistaken for metastatic tumor.

Electron microscopy has demonstrated both lipids and excessive glycogen within the clear cells. Furthermore, cytoplasmic organelles, especially the rough endoplasmic reticulum, were reduced compared to typical hepatocellular carcinoma (Wu et al., 1983).

Differential Diagnosis. The major histologic problem is exclusion of metastatic clear cell carcinoma from the kidney or adrenal. If adequate tissue is available for study, transition to typical hepatocellular carcinoma is noted. However, an occasional case or small biopsy may not have traceability and thus no distinction may be made. Although metastasis of hepatocellular carcinoma to kidney is rare, two (non-clear cell type) hepatocellular carcinoma patients in our series had coexistent renal cell carcinoma. In addition, one patient with clear cell hepatocellular carcinoma in our series had a clear cell renal carcinoma as well, and was classified as such because of the traceability of the clear cell hepatocellular carcinoma to typical hepatocellular carcinoma. Metastasis of renal cell carcinoma to liver is common and occurs in one-third to one-fourth of renal cancer patients.

Prognosis. Clear cell hepatocellular carcinoma has been associated with a better prognosis based on the Hong Kong series (Lai et al.). Eighty patients with hepatocellular carcinoma were analyzed and the 50 percent survival rate was 3.5

weeks for the entire group; yet for the clear cell hepatocellular carcinoma, the survival was 14 weeks if diffuse clear cell change was present. Such improved survival has not been noted in our material or in other series, but the presence of clear cell hepatocellular carcinoma may be lower in other populations compared to Hong Kong.

Giant Cell Carcinoma

Definition. Giant cell hepatocellular carcinoma applies to the hepatocellular carcinoma with more than 50 percent of the primary tumor composed of giant cells (either multinucleated or pleomorphic large cells).

Pathology. Multinucleated giant cells are common in some hepatocellular carcinomas (especially grades III and IV) and occasionally may comprise a significant part of the entire tumor. The multinucleated cells may be either benign appearing (osteoclastoma type) with abundant cytoplasm and many small nuclei (figs. 231, 232) or bizarre giant cells (pleomorphic type) with large pleomorphic nuclei containing large and multiple nucleoli and less cytoplasm (fig. 233). The osteoclastoma giant cells are 30 to 200 μ in diameter and contain more than 100 nuclei. In the pleomorphic variant, the cells have more variation in nuclear features, are not as large as in the osteoclastoma variant, and often display phagocytosis and polygonal spindle cells in the stroma. Some of the giant cell tumors have a wide variation in cell size and have both osteoclastoma and pleomorphic giant cells with phagocytosis (Andreola et al.). In the rare example in which no typical hepatocellular carcinoma is noted and the cells have eosinophilic cytoplasm but no bile, glycogen or hyaline, the liver is considered the primary site once a thorough search (such as an autopsy) has excluded other sites (Kuwano et al.; Munoz et al.). Origin of giant cell hepatocellular carcinoma from a large cyst wall was documented in one patient of our series.

Pathogenesis. The cell of origin is not apparent and Munoz and associates favored a Kupffer cell origin because of phagocytosis by tumor cells. Others have studied pancreatic giant cell tumors and concluded that the ultrastructural evidence favored an epithelial origin (Rosai). We favor a hepatocellular origin because many hepatocellular carcinomas of typical histology have some giant cell components and these osteoclastoma-like tumors often arise in cirrhosis, as do most hepatocellular carcinomas.

Differential Diagnosis. The differential diagnosis of a giant cell hepatic tumor includes metastatic tumors such as melanoma, choriocarcinoma, rhabdomyosarcoma, giant cell carcinoma from another primary location (lung, pancreas, thyroid, etc.), anaplastic squamous carcinoma, and malignant fibrous histiocytoma. Final diagnosis may require a thorough search for another primary tumor and many special stains to rule out the considerations listed above.

Combined Hepatocellular Carcinoma

Combined hepatocellular carcinoma is the term preferred for a tumor containing both hepatocellular carcinoma and distinct or separate cholangiocarcinoma. Ductal transformation of hepatocellular carcinoma occurred in 5 to 10 percent of the hepatocellular carcinomas in our series,

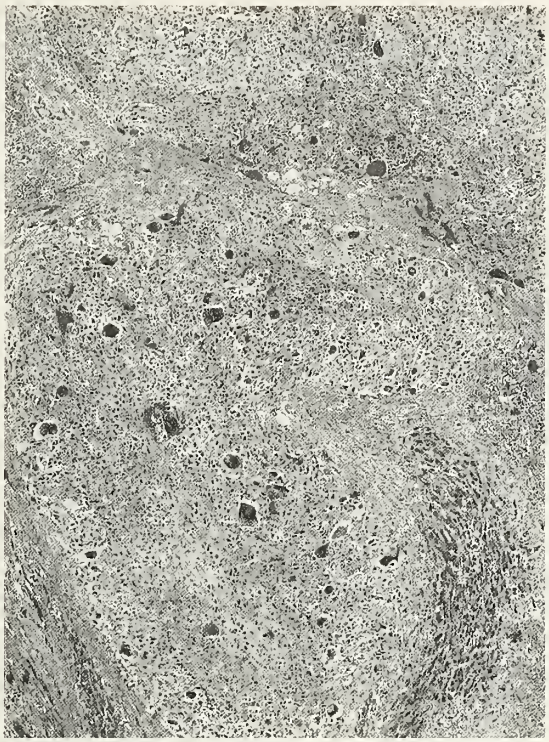


Figure 231
(Figures 231 and 232 are from the same patient)
GIANT CELL CARCINOMA
This giant cell hepatocellular carcinoma (osteoclastoma type) has a few multinucleated giant cells scattered among smaller pleomorphic cells with eosinophilic cytoplasm. X125. (Courtesy of Dr. J.K. Reddy, Chicago, Illinois.)

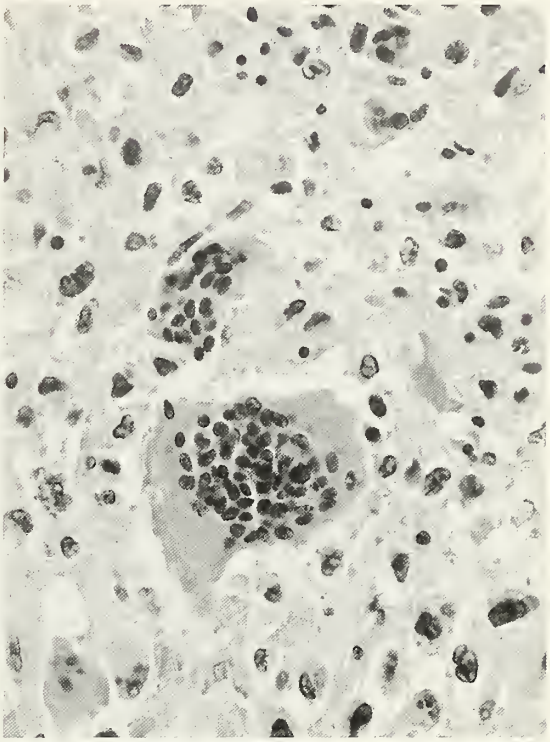


Figure 232
GIANT CELL CARCINOMA
These osteoclastoma giant cells have many small nuclei without variation in chromatin, and nucleoli are not present. X1240. (Courtesy of Dr. J.K. Reddy, Chicago, Illinois.)

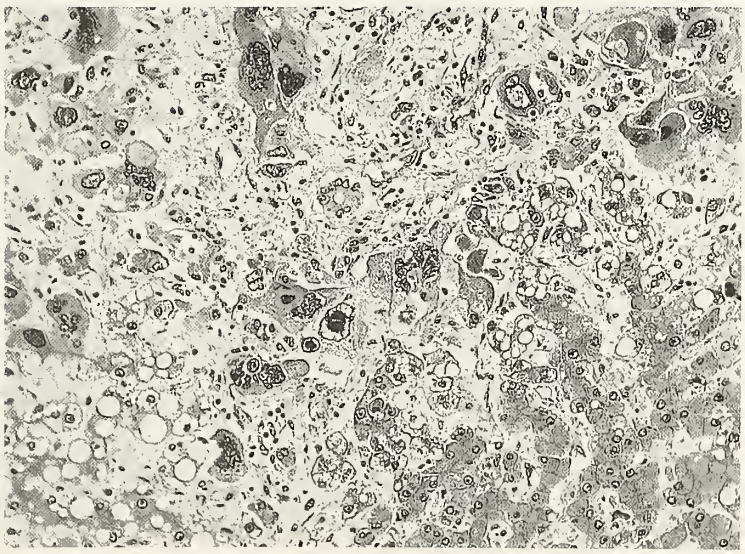


Figure 233
GIANT CELL CARCINOMA
There is marked variation in nuclear size and shape in this pleomorphic giant cell hepatocellular carcinoma. X365.

although the ductal areas were very small in many tumors. Occasionally, two major tumor masses, a typical hepatocellular carcinoma and a cholangiocarcinoma, were found in the liver. The term mixed hepatic tumor is recommended for a hepatocellular carcinoma with a mesenchymal component and is not applied to the tumor with two varieties of epithelial tumors. In a review of combined hepatocellular carcinoma/cholangiocarcinoma, Goodman and colleagues described four patients without transition forms from the hepatocellular carcinoma to the glandular cholangiocarcinoma. Twelve cases in Goodman's series were classified as transition cases because of apparent transition of hepatocellular carcinoma to glandular adenocarcinoma. Histochemistry demonstrated mucin production by the glandular component. In their review of histologic and immunohistochemical features, Goodman and associates noted that keratin was a good marker of biliary differentiation, but other markers such as α-1-antitrypsin, fibrinogen, IgG, and carcinoembryonic antigen were identified in both hepatocellular carcinomas and cholangiocarcinomas. Expression of ABH and Lewis blood group antigens were studied in five combined hepatocellular carcinoma/ cholangiocarcinomas and the pattern of expression was similar only to hepatocellular carcinoma (Okada et al.). Therefore, some combined hepatocellular carcinoma/cholangiocarcinomas may be variants of hepatocellular carcinoma similar to spindle cell carcinoma/hepatocellular carcinomas. Additional proof by hepatitis B virus integration in combined hepatocellular carcinoma/ cholangiocarcinomas may be helpful in explaining the dual histologic appearance. Some pure hepatocellular carcinomas may produce a combined pattern in metastasis (Wada et al.).

Pathology. The parenchyma of hepatocellular carcinoma and cholangiocarcinoma are different; the cholangiocarcinoma has a firmer texture than hepatocellular carcinoma, which also may have bile staining, focal necrosis, and a finely granular texture (fig. 234). Between the two extremes of firmness and softness, the tumor has transition areas in both texture and histologic appearance.

Hormonally Active Hepatocellular Carcinoma

Hormonal activity of hepatocellular carcinoma has brought some patients to medical attention. Intractable watery diarrhea ceased after resection of a typical hepatocellular carcinoma from a 44 year old woman (Steiner et al.). However, because carcinoid tumor may be mistaken for hepatocellular carcinoma by light microscopy, special stains, including chromogranin, and selected hormone stains must be performed if there are clinical symptoms of carcinoid syndrome. Furthermore, review of the published photographs suggests that some of these tumors may not be hepatocellular carcinomas, but may be primary hepatic neuroendocrine tumors. The presence of typical hepatocellular carcinoma architecture (i.e., trabeculae) and cytologic features of hepatocytes are often absent. These tumors frequently lack trabecular growth with prominent sinusoidal lining cells, nuclei with prominent large nucleoli, and bile production. However, the watery diarrhea syndrome does occur with hepatocellular carcinoma as the histologic features of the report by Steiner and associates are typical of hepatocellular carcinoma (Bonfiglio).

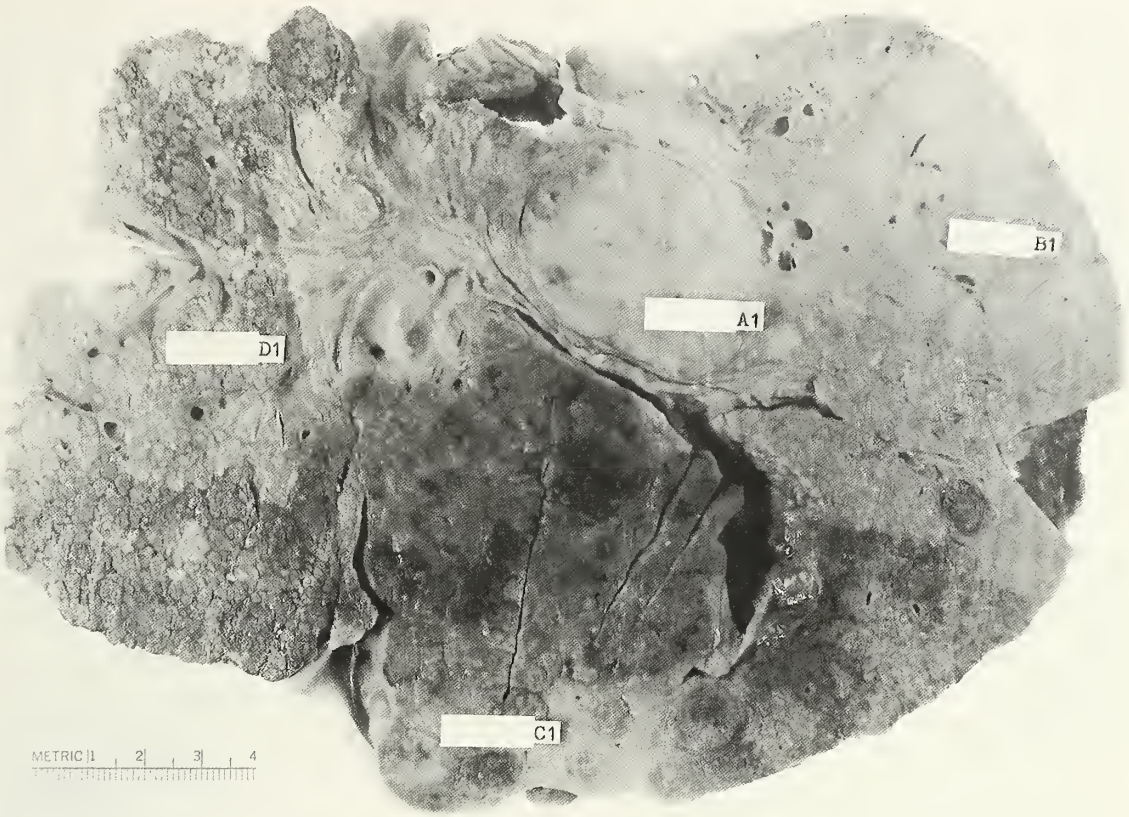


Figure 234
(Figures 234, 227, and 228 are from the same patient)
COMBINED HEPATOCELLULAR CARCINOMA

The cut surface of this combined spindle cell hepatocellular carcinoma, trabecular hepatocellular carcinoma, and cholangiocarcinoma that developed in cirrhosis has different textures for each type. The firmest area (A) is a spindle cell hepatocellular carcinoma with very bland fibrous stroma. The cholangiocarcinoma area (B) is multinodular, but firm and gray-white. The hepatocellular carcinoma (C) is recognized by the green color typical of bile staining. (Courtesy of Dr. S. Govindarajan, Downey, California.)

Carcinosarcoma

With too few sections examined to show the transition of the spindle cell areas to typical hepatocellular carcinoma, many of the tumors classified as carcinosarcoma may actually be spindle cell hepatocellular carcinoma. Because spindle cell hepatocellular carcinoma is a recognized entity, we recommend that the term carcinosarcoma be reserved for the liver with both hepatocellular carcinoma and a nonspindle cell sarcoma, such as osteosarcoma, chondrosarcoma, angiosarcoma or malignant schwannoma, etc. Simultaneous hepatocellular carcinoma and chondrosarcoma have been reported (Sonoda et al.) and most of the previously reported carcinosarcomas are described as spindle cell sarcoma without further differentiation.

However, because spindle cell metaplasia is common for many carcinomas, more specialized differentiation (such as osteoid formation) may be utilized as a criterion for the diagnosis of sarcoma in the presence of carcinoma. Carcinosarcoma of the colon may be admixed with sarcomatous differentiation including osseous, cartilage, and nonspecific spindle cell differentiation (Weidner and Zekan). Therefore, even with divergent sarcomatous patterns with carcinoma, a carcinosarcoma may not be two separate tumors, but may reflect the extreme in metaplasia. The most convincing examples of carcinosarcoma are two separate tumor masses with no physical continuity, one having a typical epithelial differentiation such as hepatocellular carcinoma and the other being a recognizable sarcoma such as osteosarcoma or chondrosarcoma.

SCLEROSING HEPATIC CARCINOMA

SYNONYMS AND RELATED TERMS: Fibrosing hepatocellular carcinoma; cholangiocarcinoma with hypercalcemia.

Definition. Sclerosing hepatic carcinoma is applied to a primary hepatic carcinoma with abundant fibrosis and an epithelial component that is duct-like but has eosinophilic cytoplasm.

Incidence. Sclerosing hepatic carcinoma was identified in 15 of 462 primary hepatic malignant epithelial tumors in the LACUSC-MC and USC Liver Unit autopsy series and in 10 of 258 primary hepatic malignant epithelial tumors of the county-wide hospital survey (approximately 3 percent of all primary hepatic tumors, excluding hemangiomas).

Clinical. Sclerosing hepatic carcinoma occurs equally in males and females, similar to peripheral cholangiocarcinoma. The mean age was 62.7 years, 7.6 years older than the hepatocellular carcinoma group in the USC series (Omata et al.). Clinical symptoms were not specific and included abdominal pain, swelling, and weight loss. Hypercalcemia was present in 70 percent with a mean serum calcium of 12.1 mg/dl.

Pathogenesis. The mechanism for the hypercalcemia appears to be tumor hormone production which increases bone resorption and is not mediated by the parathyroid gland. The cell of origin appears to be hepatocellular by light and electron microscopy, but markers for neuroendocrine differentiation have not been applied.

Pathology. Sclerosing hepatic carcinoma has a dry, hard, pearl-gray surface and often has a serrated margin. The borders may be fleshy and glistening, whereas the center is retracted and acellular (fig. 235). The microscopic features are variable and extend from duct cells with marked hepatocellular carcinoma appearance (i.e., eosinophilic cytoplasm and nuclei with nucleoli) to cholangiocarcinoma, which has no nucleoli and very minimal cytoplasm. The fibrosis divides the duct-like epithelial clusters into small groups and large sheets are not noted (fig. 236). At the periphery, the cells tend to be more like hepatocellular carcinoma with nucleoli, more abundant cytoplasm, and sometimes bile production (figs. 237, 238). In the center of the tumor the cells have less cytoplasm and small lacunae apparently form the site of duct-like cells that have been "choked" by the dense fibrosis (fig. 239). Many of these tumors may be cholangiosarcomas, but the diagnostic areas may be missed as a result of limited sampling. Secretory granules have been

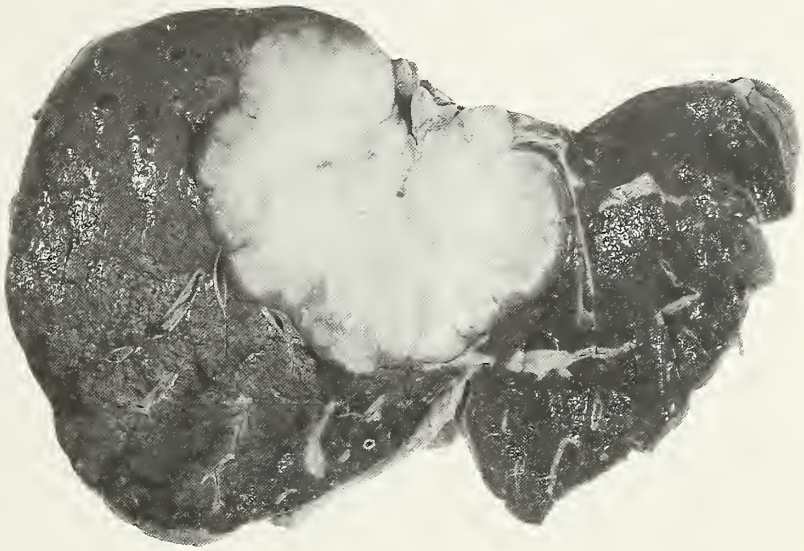


Figure 235
SCLEROSING HEPATIC CARCINOMA

A 46 year old woman with Budd-Chiari syndrome 1 year before death had marked hypercalcemia and had a sclerosing hepatic carcinoma at autopsy. A hard, fibrous, pearl-gray tumor was present at the hepatic venous outflow area and the liver was not cirrhotic.

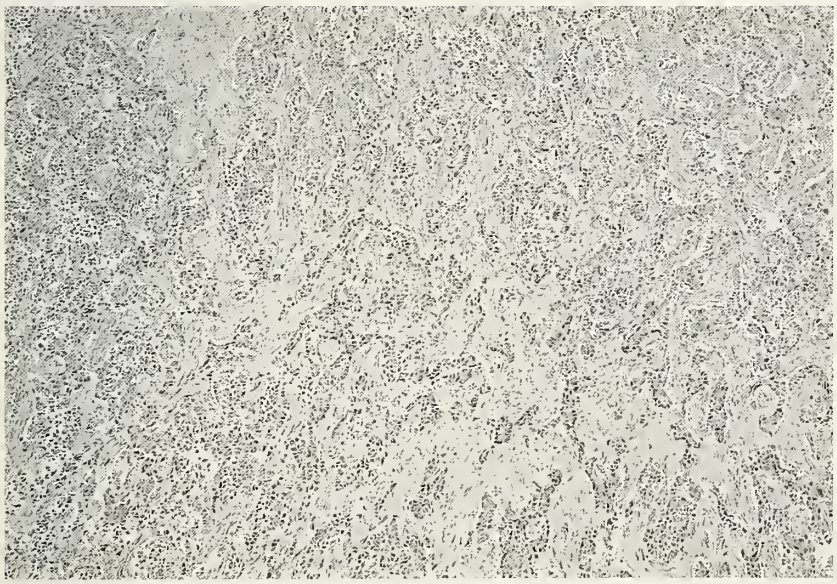


Figure 236
SCLEROSING HEPATIC CARCINOMA

The even mixture of fibrous strands and thin cords of duct-like eosinophilic cells is noted in this sclerosing hepatic carcinoma. X130.

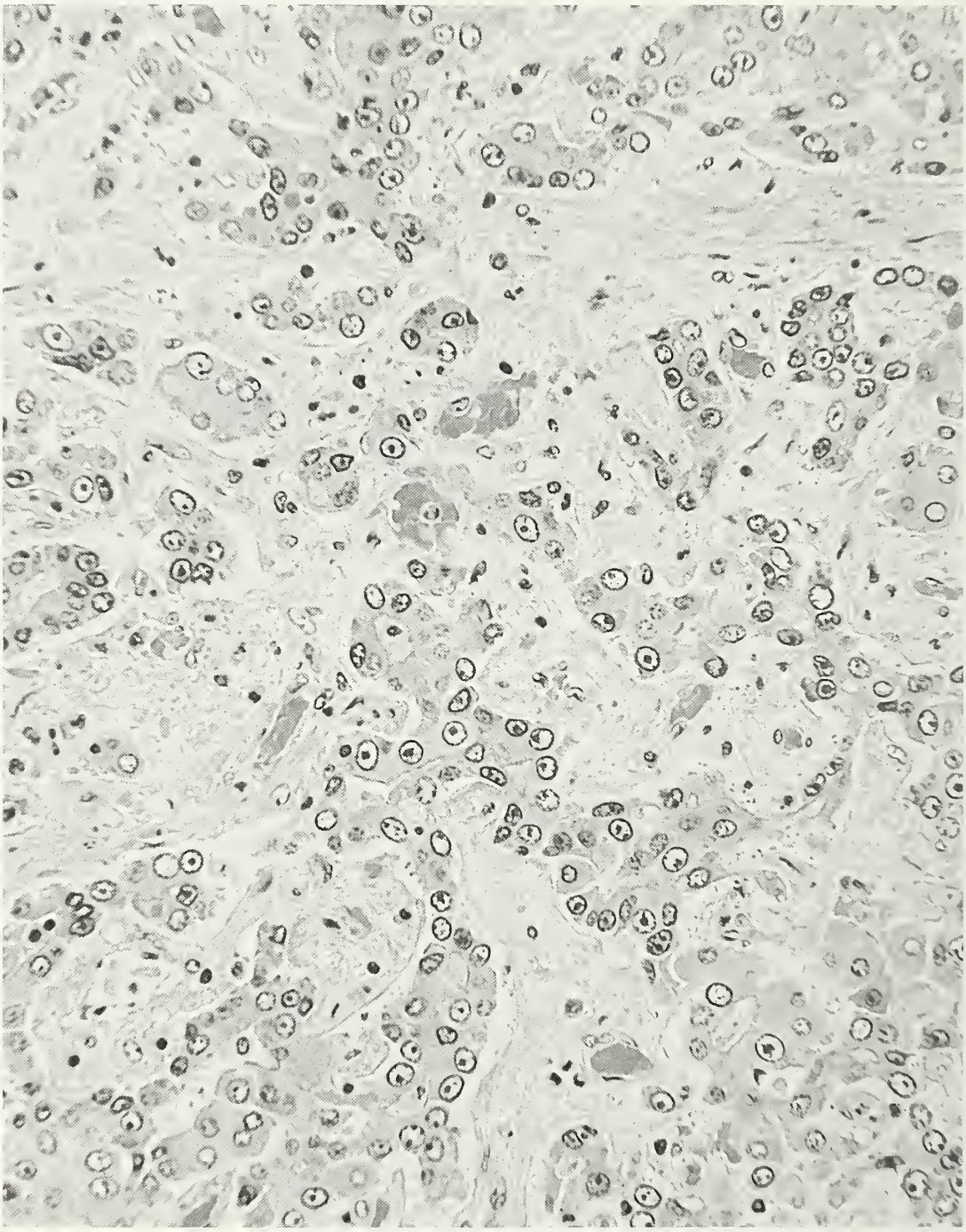


Figure 237
SCLEROSING HEPATIC CARCINOMA
The prominent eosinophilic cytoplasm and presence of nucleoli in the duct-like growth of this tumor are typical of sclerosing hepatic carcinoma. X380.

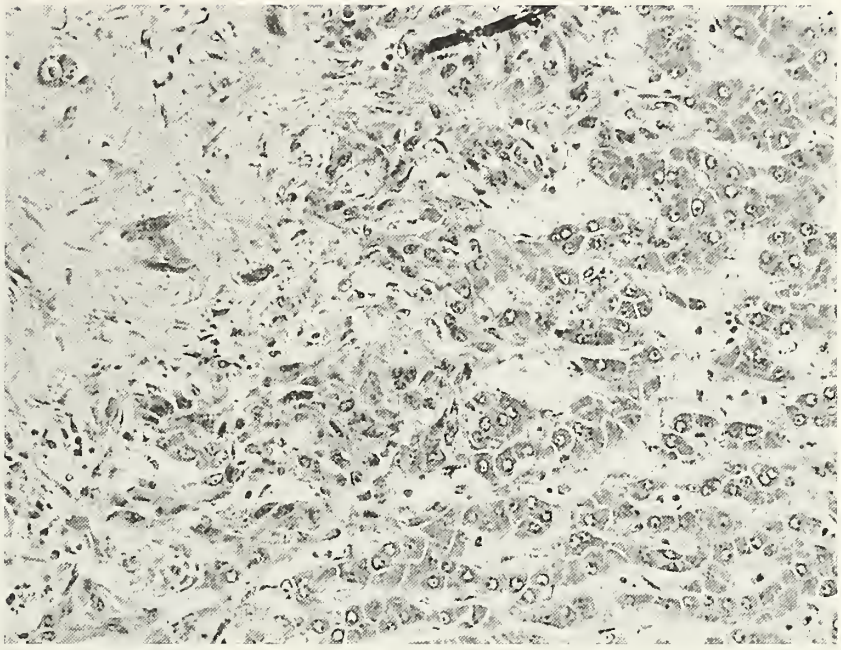


Figure 238
(Figures 238 and 239 are from the same patient)
SCLEROSING HEPATIC CARCINOMA
Near the periphery of this sclerosing hepatic carcinoma, the epithelial cells resemble hepatocytes with more cytoplasm and prominent nucleoli. X235.

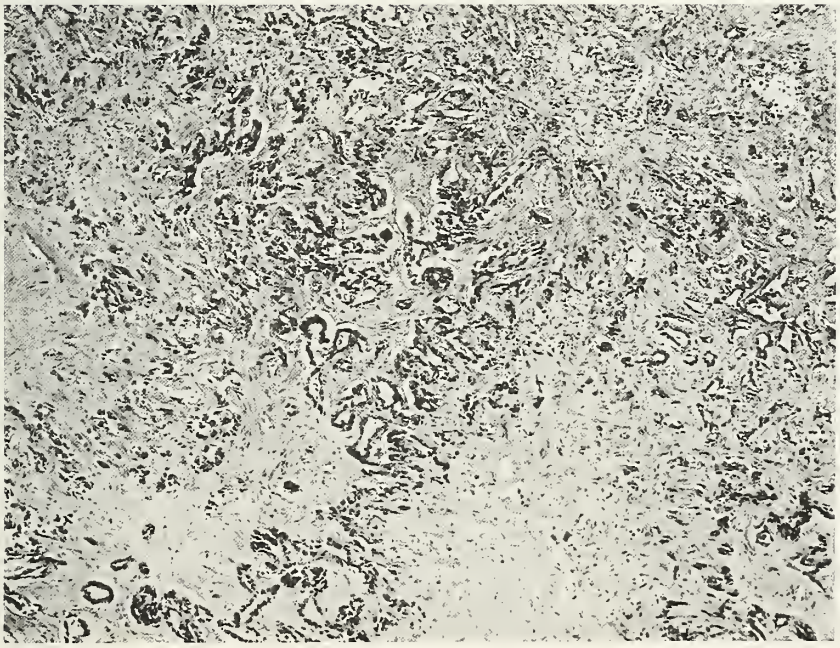


Figure 239
SCLEROSING HEPATIC CARCINOMA
In this sclerosing hepatic carcinoma, small duct-like structures with lumina are embedded within dense fibrosis in the intermediate zone (i.e., not the center and not the periphery). X70.

identified in three of four sclerosing hepatic carcinomas studied by electron microscopy in our series (fig. 240).

Prognosis. The metastatic pattern of sclerosing hepatic carcinoma is more similar to peripheral cholangiocarcinoma than to hepatocellular carcinoma (see Table 11), as only 20 percent of the cases had metastasis at autopsy, primarily in the portal lymph nodes and not bone.

Differential Diagnosis. Metastatic adenocarcinoma can mimic sclerosing hepatic carcinoma so well that all the biopsies available in our patients were mistaken for metastatic adenocarcinoma. The histologic features are very similar and if eosinophilic cytoplasm and prominent nucleoli are noted in a sclerosing tumor, then sclerosing hepatic carcinoma may be considered. If hypercalcemia is present and no other primary with metastasis is known, then sclerosing hepatic carcinoma is very likely.

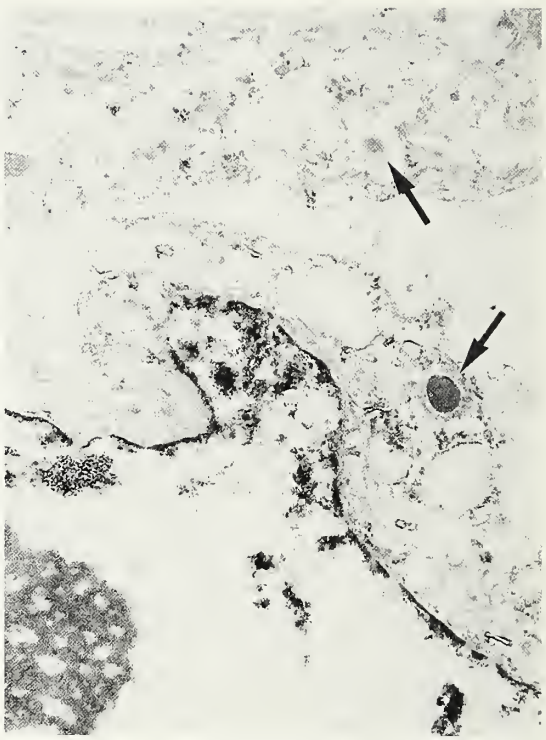


Figure 240
SCLEROSING HEPATIC CARCINOMA
An epithelial cell in a sclerosing hepatic carcinoma and an occasional secretory granule (arrows) are illustrated. X85,250.

HEPATOBLASTOMA

SYNONYMS AND RELATED TERMS: Hepatic mixed tumor of childhood; malignant hepatoblastoma; epithelial and mesenchymal hepatoblastoma.

Definition. Hepatoblastoma is a malignant tumor of embryonic or fetal hepatocytes that often has mesenchymal elements and occurs prior to 3 years of age.

Incidence. Hepatoblastoma is the most common primary hepatic tumor in childhood and accounts for approximately 43 percent of all primary hepatic tumors summarized from 11 large series (totalling 1237 patients) from many countries (Weinberg and Finegold). Hepatoblastoma is responsible for 50 percent of all primary hepatic tumors requiring surgery in a 10 year period in the survey of U.S. pediatric surgeons (Exelby et al.). Hepatoblastoma is about one-tenth as frequent as Wilms tumor and generally accounts for 0.2 to 5.8 percent of childhood malignant tumors (Ishak and Glunz).

Clinical. The age range for hepatoblastoma at diagnosis is a few hours after birth to 3 years, with the average age of 17 months; the majority of tumors are recognized prior to 2 years (Gonzalez-Crussi et al.; Lack et al., 1982). There is a male predominance (2:1) and Caucasians seem to be afflicted more often than others (Fraumeni et al.; Ishak and Glunz). The

clinical diagnosis is often directed to the cause of hepatomegaly, abdominal swelling or acute abdomen (due to rupture in 2 of 54 patients in the 1982 series of Lack and associates). Metabolic effects of hepatoblastomas are striking and include osteopenia (10 of 54 patients in the 1982 series of Lack and associates) with bone fracture in some children, hypoglycemia, isosexual precocity (2 of 54 patients in the 1982 series of Lack and associates), and hemihypertrophy on the left side. Virilizing effects of hepatoblastoma may be noted prior to the hepatic tumor or even recognized upon recurrence and these changes may not be rare; currently 25 patients have been reported (Nakagawara et al.). Elevation of β-HCG correlates with virilization (Morinaga et al.). Moderate to marked thrombocytosis occurred in 10 of 54 patients (Lack et al., 1982) with some platelet counts above 1 million/mm^3. The serum α-fetoprotein is elevated in 80 to 90 percent of the cases and is helpful in monitoring recurrence, but is not always reliable. Cystathioninuria has been noted in several patients. Radiographic examination may show calcification of the hepatic tumor and, possibly, metastatic disease in the lung.

Pathogenesis. A specific etiology of hepatoblastoma is not apparent and hepatitis B virus does not seem to play a role. Familial occurrence is rare but notedand an association with familial polyposis coli has been reported (Fraumeni et al.; Li et al.; Napoli and Campbell). Metabolic disorders, although predisposing to hepatocellular carcinoma, do not seem related to hepatoblastoma. The variation in incidence in the United States suggested environmental factors (Fraumeni et al.) and there are scattered reports of drug effects including fetal alcohol syndrome, oral contraceptive use, and sterility drug treatment (Khan et al.; Melamed et al.; Otten et al.). Since up to 30 percent of patients have a congenital anomaly, a developmental anomaly has been suggested as the etiologic factor in hepatoblastoma (Lack et al. 1982).

The derivation of the mesenchymal component has been controversial as some have suggested hepatoblastoma is a mixed tumor of malignant epithelial and malignant mesenchymal components derived from different cells. However, use of cultured hepatic cells derived from chemically induced malignant tumors in rats suggested that the mesenchymal component may be a metaplastic element (Tsao and Grisham). The metastatic lesions, although predominantly epithelial, are also noted to contain osteoid, leading us to believe the two elements are of common origin. Abenoza and associates studied the ultrastructural and immunohistochemical features of 19 hepatoblastomas. The positive reaction for cytokeratin by the spindle cell component adjacent to the osteoid indicated the mesenchymal component was probably metaplastic.

Pathology. Even though the clinical symptoms are usually present only for a few weeks prior to diagnosis, most hepatoblastomas are rather large at the time of diagnosis, with a size range of 3 to 20 cm in diameter and an average size of 10 to 12 cm in diameter. The weight of the tumor may be massive, up to 25 times the estimated weight of the normal liver the hepatoblastoma replaced (Ishak and Glunz). Cirrhosis is absent. Typical resection specimens are 290 to 1300 g. The right lobe is more frequently involved (60 percent) and both lobes have tumors in

one-third of the cases. A solitary mass is usual but multinodularity is common (figs. 241, 242) (Kasai and Watanabe). The cut surface is variegated with hemorrhage and necrosis more common in the mixed type and the solid gray area corresponds to the pure epithelial areas. Osteoid changes are usually not grossly apparent (Lack et al., 1982).

Histologic variation is typical in hepatoblastoma and the various subtypes are noted in a single field (fig. 243). Several subtypes are recognized including fetal, embryonal, anaplastic, and mixed (epithelial and mesenchymal). A pure epithelial component is the most common type, although a few authorities have indicated that if enough sections are examined, mesenchymal elements may be identified. The conventional hepatoblastoma (in contrast to the recently recognized anaplastic subtype) has only an epithelial component (60 percent) or a mixed epithelial-mesenchymal component (30 percent) or is unclassified (10 percent). The epithelial element may be subdivided into fetal and embryonal subtypes. The fetal subtype is composed of cells smaller than normal hepatocytes, cells with a relatively low nucleus/cytoplasm ratio (1/2 to 1/4), eosinophilic cytoplasm, nucleoli, few mitoses, and a growth pattern that may have variation due to differences in cytoplasmic glycogen storage (fig. 244). Extramedullary hematopoiesis is common in this subtype. A trabecular or compact growth pattern is formed and an endothelial sheath of the trabeculae is present. Transition of fetal to embryonal subtypes may be gradual or sharp (pl. IX-B). Embryonal hepatoblastoma cells have a higher nucleus/cytoplasm ratio (1/1 to 1/2), basophilic cytoplasm, and appear to have a higher density. The growth pattern may be trabecular or compact and may be sheets of cells (fig. 245). Some ductal elements occur and squamous differentiation may be noted.

The mesenchymal elements are usually osteoid, chondroid or spindle cells. The osteoid may appear in stromal or epithelial areas (fig. 246). If the osteoid is surrounded by spindle cells, it resembles osteosarcoma. Osteoid is less common in metastasis but does occur. Melanin-like pigment was noted in one of our patients (fig. 247).

The anaplastic variant has recently been considered separately because of a poorer prognosis. Usually, hepatoblastoma is circumscribed, but often the anaplastic subtype has infiltration at the borders and incorporation of adjacent hepatocytes and bile ducts in the tumor. This subtype is composed of loosely cohesive, monomorphous cells with scant cytoplasm and a high mitotic rate. In four of five patients in the series of Lack and associates (1982), a conventional epithelial pattern was also present. Vascular invasion is noted in one-half of the conventional hepatoblastomas, but occurs in all the anaplastic hepatoblastomas (Lack et al., 1982).

Electron microscopy has demonstrated that hepatoblastoma cells have some hepatocellular features, but many are primitive with few organelles. The fetal cells have a rough endoplasmic reticulum and the bile canaliculi have microvilli, but nuclear folds, which are common in hepatocellular carcinoma, are lacking (Horie et al.).

Figure 241
HEPATOBLASTOMA

This multinodular hepatoblastoma in an 11 month old male has bile staining (dark areas) and fatty change (light areas), as well as focal calcification. The remaining liver is normal. (Fig. 89 from Fascicle 25, First Series.)

Figure 242
HEPATOBLASTOMA

This recurrent hepatoblastoma seen at autopsy nearly replaced the entire liver with a variegated pale tan and gray tumor in a 1 year old male whose left lobe was resected at age 6 months due to a 370 g solitary mass. A recurrent tumor was detected within 2 months of surgery and the serum α-fetoprotein was again elevated. Metastatic tumor was present in the lungs.

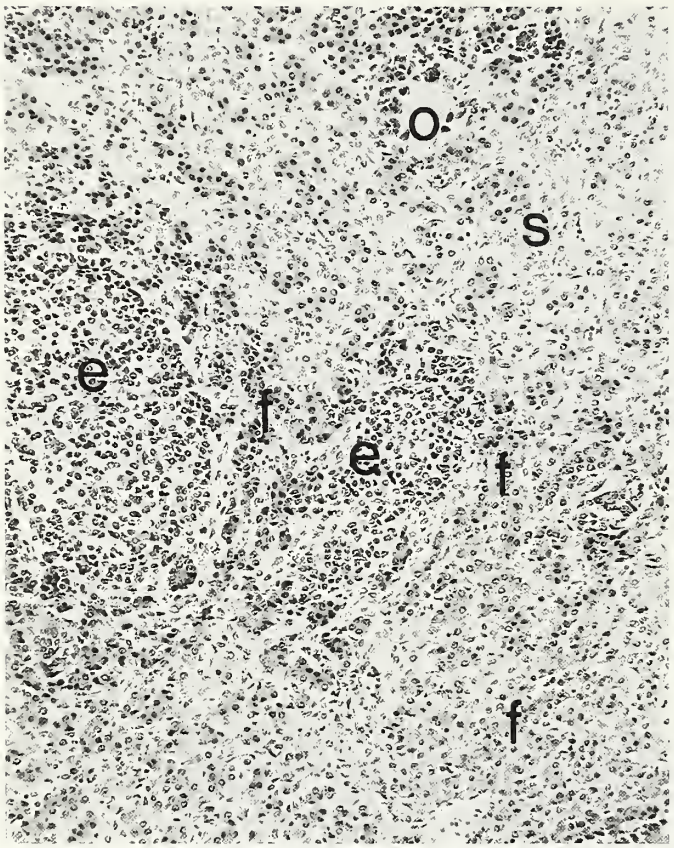


Figure 243
(Figures 243 and 244 are from the same patient)
HEPATOBLASTOMA
This hepatoblastoma has a mixture of patterns including fetal (f), embryonal (e), stromal (s) tissue, and a small area of osteoid (o). The fetal cells are eosinophilic with one area that shows clear cytoplasm and loosley arranged embryonal cells. X70.

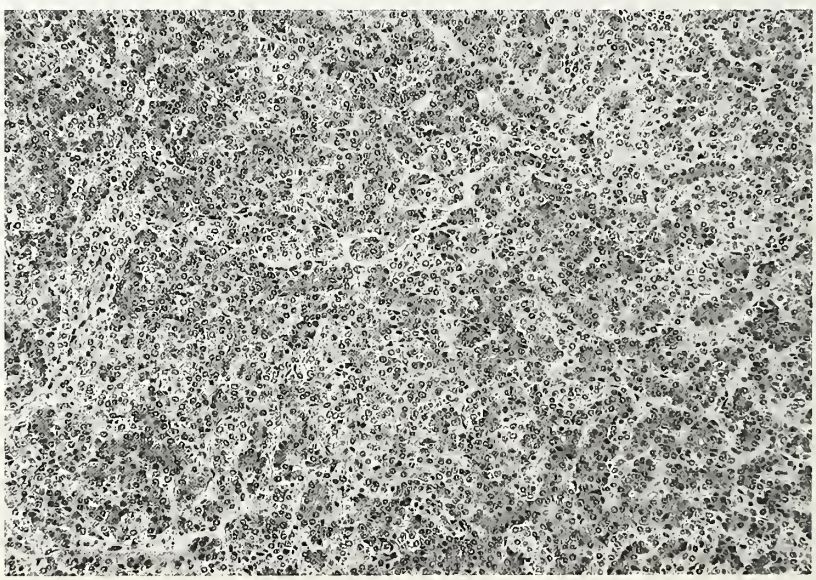


Figure 244
HEPATOBLASTOMA
This hepatoblastoma has a mixture of patterns including embryonal areas (basophilic cells with little cytoplasm) and fetal cells (more cytoplasm that is eosinophilic and with cord arrangement). X117.

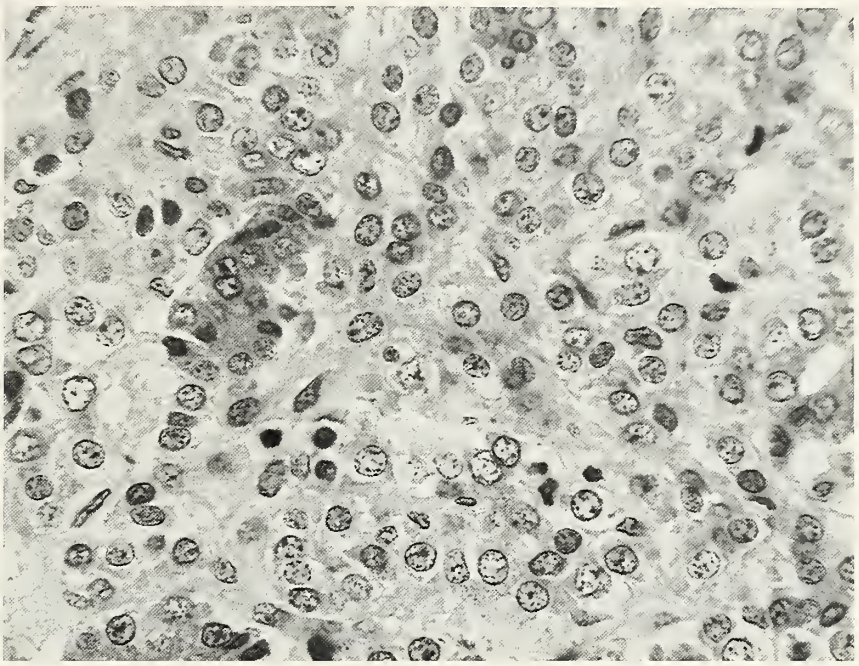


Figure 245
(Figure 245 and Plate IX-B are from the same patient)
HEPATOBLASTOMA
This hepatoblastoma has a predominantly embryonal carcinoma subtype and a small area of fetal cells (with more cytoplasm). X585. (Courtesy of Dr. Robert Hutter, Livingston, New Jersey.)

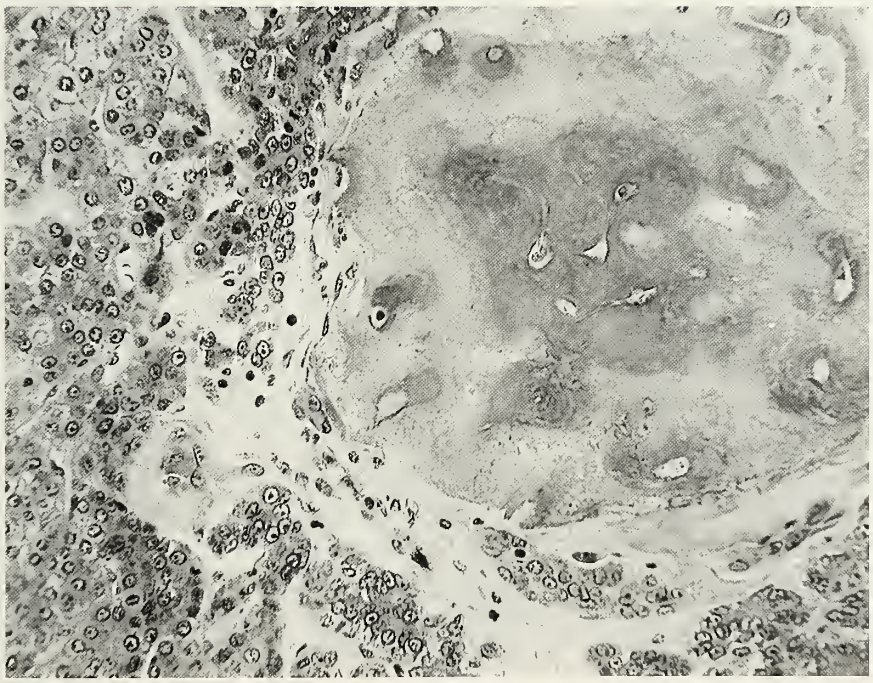


Figure 246
HEPATOBLASTOMA
This figure illustrates lung metastasis of hepatoblastoma with the osteoid and calcified tumor also containing the fetal subtype. X235. (Courtesy of Drs. Benjamin Landing and Hart Issacs, Los Angeles, California.)

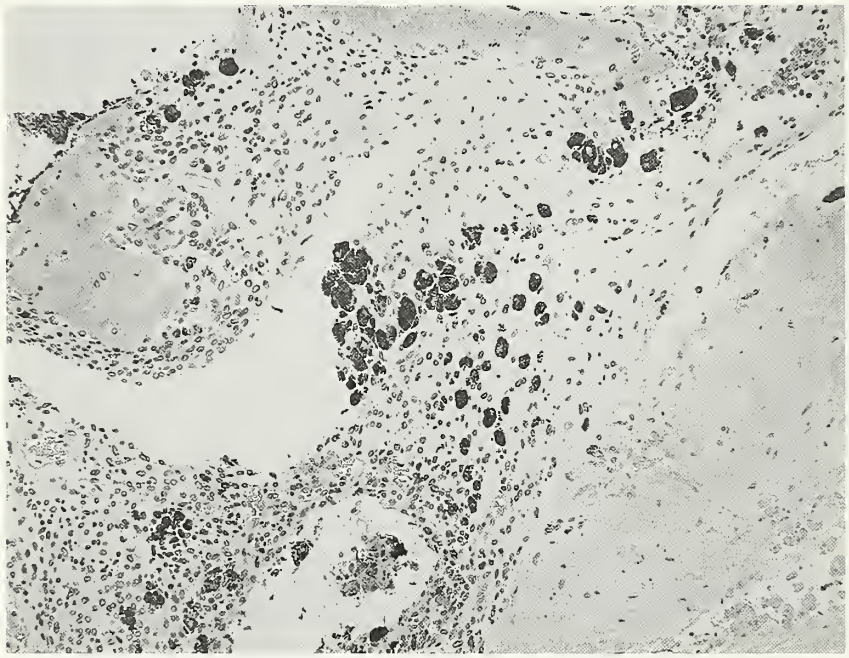


Figure 247
HEPATOBLASTOMA
This hepatoblastoma has foci of melanin pigment adjacent to osteoid, which is very unusual. X117. (Courtesy of Drs. Benjamin Landing and Hart Issacs, Los Angeles, California.)

Variants. Mucoid anaplastic hepatoblastoma is recognized by abundant mucoid material which produces a slimy, gelatinous, gross appearance (Joshi et al.). The tumor was rapidly fatal with metastasis to the lungs and peritoneum despite resection of the primary tumor. Serum α-fetoprotein was elevated and electron microscopy suggested epithelial derivation. No recognizable features of yolk sac tumor or embryonal sarcoma were present.

Teratoid hepatoblastoma was described by Manivel and associates as a hepatoblastoma with mixed components and atypical histologic features including "embryonic" tubules, which resembled nephroblastoma or primitive neuroectodermal tumor, melanin pigment in tumor cells, and ganglion cells. Mesenchymal elements, including osteoid, were noted.

Differential Diagnosis. The differential diagnosis of hepatoblastoma includes neuroblastoma, yolk sac carcinoma, rhabdomyosarcoma, and teratocarcinoma. If material is limited, small fragments of the anaplastic or mucoid variant will resemble neuroblastoma, malignant lymphoma, and embryonal carcinoma or yolk sac carcinoma. Therefore adequate sampling, clinical correlation with other known tumors, special stains including neuron specific enolase (for neuroblastoma), and lymphocytic marker studies will usually result in a more accurate diagnosis. Metastatic sarcoma, including rhabdomyosarcoma of the extrahepatic biliary tree, may resemble the anaplastic hepatoblastoma and sampling is essential to obtain areas of conventional hepatoblastoma subtype. The presence of melanin pigment, respiratory epithelium, and intestinal epithelium has rarely been

noted and raises the question of teratomatous origin. The presence of neural elements and other mature ectodermal elements are regarded as essential for teratomatous classification.

Prognosis. In the series of Lack and associates (1982), the overall mortality of hepatoblastoma was 76 percent, with an average duration of disease of 8 months (range of 1-27 months). Surgical resection is frequent (61 percent) with long-term survival common in up to 57 percent of resected patients (Exelby et al.; Lack et al., 1982). The anaplastic variant was not associated with long-term survivors, whereas a pure fetal pattern was associated with a cure in every resected patient (Lack et al., 1982; Weinberg and Finegold). Chemotherapy may alter the course of disease, but the effect has not been impressive. Recurrence may occur up to 5 years after surgery.

CHOLANGIOCARCINOMA

SYNONYMS AND RELATED TERMS: Bile duct carcinoma; adenocarcinoma of the liver; cholangiocellular carcinoma; duct carcinoma.

Definition. Cholangiocarcinoma is a malignant tumor arising from bile duct epithelium. Clinical and pathologic features vary with the site of origin of the tumor, which may be the small portal bile duct branches (interlobular ducts), major intrahepatic bile ducts, extrahepatic bile ducts, or papillae of Vater.

Intrahepatic cholangiocarcinoma may be classified into four groups based on site of origin, each with different clinical patterns. *Peripheral cholangiocarcinoma* arises in a small bile duct branch near or within a portal area, whereas *major hepatic duct cholangiocarcinoma* arises within a major duct near the hilum. Cholangiocarcinoma arising in the right, left or common bile duct often extends into the adjacent major intrahepatic bile duct and is a *hilar cholangiocarcinoma*. A fourth category is the *intraductal papillary cholangiocarcinoma* which often appears limited to intraductal growth and, therefore, spread of the tumor is not readily noted. This pattern is also referred to as intraductal papillomatosis because of its benign appearance.

Incidence. Cholangiocarcinoma is considerably less common than hepatocellular carcinoma. It represented 9.5 percent of all malignant hepatic tumors and 8.2 percent of all primary hepatic tumors in our autopsy series (see Table 1). In the large national study from Japan, cholangiocarcinoma was responsible for 8 percent of primary adult epithelial hepatic tumors (Okuda and the Liver Cancer Study Group of Japan). Reported incidence of cholangiocarcinoma versus hepatocellular carcinoma varies around the world from 5 to 30 percent (Mori and Nagasako). Some variation in incidence may be due to differences in histologic interpretation because some cholangiocarcinomas resemble hepatocellular carcinomas. We have placed most sclerotic carcinomas in the category of sclerosing hepatic carcinoma (distinct from cholangiocarcinoma) because of specific histologic and clinical features.

Worldwide distribution of cholangiocarcinoma is not well-known because the reporting system commonly in use records all primary hepatic tumors into one category. Furthermore, because cholangiocarcinoma mimics the histologic features of metastatic adenocarcinoma, an autopsy is required to confirm the diagnosis of cholangiocarcinoma, and this confirmation is often lacking.

In some countries, particularly the Orient, cholangiocarcinomas are reported in larger numbers than in the Western Hemisphere (Belamaric; Flavell; Hou, 1956; Okuda and the Liver Cancer Study Group of Japan). Furthermore, in areas endemic for Opisthorchis, such as Thailand, cholangiocarcinoma is the leading cause of cholestasis due to malignant tumor and is more common than pancreatic carcinoma (Juttijudata et al.). In spite of a substantial Oriental population in the Los Angeles area, we have not noted an increased incidence of cholangiocarcinoma in the Oriental immigrants and have a single example of Clonorchis associated cholangiocarcinoma in a Chinese male immigrant. The relative incidence of the four types of cholangiocarcinomas in our autopsy series is noted in Table 12.

Clinical. The age of patients with cholangiocarcinoma averages from 50 to 60 years in most series and discovery under the age of 40 years is rare (Mori and Nagasako); our youngest patient was 26 years of age and had a chronic inflammatory bowel disease. An average age of 59.2 years for cholangiocarcinoma was reported for the large national Japanese survey (Okuda and the Liver Cancer Study Group of Japan). Nearly equal sex incidence is noted, in contrast to the male predominance of hepatocellular carcinoma, although the ratio was 2:0 (male: female) for the large Japanese series (Okuda and the Liver Cancer Study Group of Japan). Clinical signs and symptoms are related to the site of origin of the tumor. Peripheral cholangiocarcinoma rarely produces any symptoms until it is far advanced and may be missed during first surgery, as opposed to lesions arising from the hilum which produce jaundice early (Klatskin). Cholangiocarcinoma arising at a major bile duct may progress for some time as the uninvolved liver clears the bile regurgitation due to the unilateral obstruction. Thus, clinical symptoms are delayed until the tumor is massive or grows to obstruct both ducts. Intraductal papillary cholangiocarcinoma produces jaundice fairly early and surgery is needed for relief of the jaundice.

Laboratory studies of patients with cholangiocarcinoma reveal that the serum bilirubin is increased and averages 15 mg percent in hilar cholangiocarcinoma versus 5.5 mg percent in peripheral cholangiocarcinoma (Okuda et al., 1977a). Serum α-fetoprotein is increased in a few (6 of 33) patients with cholangiocarcinoma and may be markedly elevated (Okuda et

Table 12

RELATIVE INCIDENCE OF CHOLANGIOCARCINOMA BY TYPE (USC Autopsy Series)

Type	Number	Male:Female	Age
Peripheral cholangiocarcinoma	30	19:11	61 years
Major duct cholangiocarcinoma	4	2:2	–
Hilar cholangiocarcinoma	10	7:3	–
Intraductal papillary cholangiocarcinoma	0	0	0

al., 1977a). Hepatitis B virus studies have been negative. Serum carcinoembryonic antigen is elevated in 75 percent of the cases (Kawarada and Mizumoto). In contrast to hepatocellular carcinoma, paraneoplastic syndromes are not common in cholangiocarcinoma. Hypercalcemia was noted in one of our patients with major duct cholangiocarcinoma, but this is much more common in sclerosing hepatic carcinoma (Omata et al.).

Pathogenesis. Several predisposing factors are known. Twenty percent of our autopsy series (1918-1982) had some predisposing factor, of which benign simple cysts or von Meyenberg complexes were the most common. Because such small cysts are not well-documented in the liver at autopsy, the association in our series is not reliable. Reported predisposing factors for development of cholangiocarcinoma include cystic disorders, inflammatory bowel disease and primary sclerosing cholangitis, intrahepatic calculi, parasitic infestation, cirrhosis, toxins such as Thorotrast, and drugs such as oxymetholone. In the largest single series (Okuda et al., 1977a), associated conditions included cholelithiasis (10 of 57 cases) and cystic liver disease (2 of 57 cases), but no clonorchiasis, even though 22 cases were from endemic areas.

Cystic duct anomalies associated with cholangiocarcinoma include von Meyenberg complexes (Homer et al.), congenital hepatic fibrosis (Daroca et al.; Parker), hepatic cysts (Azizah and Paradinas; Bloustein; Willis), Caroli's disease (Gallagher et al.; Jones and Shreeve), and choledochal cysts (Alonso-Lej et al.; Flanigan). In our material, 16 percent had some cystic lesions, whereas only 0.6 percent of our hepatocellular carcinoma patients had any cystic lesion described. Cholangiocarcinoma arising in association with cystic disease is usually noted adjacent to the cysts and not arising within a cyst wall as with a cystadenocarcinoma. Choledochal cysts are associated with cholangiocarcinoma, but only one-third of these cholangiocarcinomas arise within the liver and the majority occur in the wall of the extrahepatic choledochal cyst. The mechanism of cholangiocarcinoma arising in von Meyenberg complexes is unknown as a direct extension of benign von Meyenberg complex into cholangiocarcinoma is not noted in our material, although one case has been reported (Homer et al.).

Chronic proliferative cholangitis secondary to intrahepatic calculi has been associated with development of cholangiocarcinoma (Nakanuma et al.; Okuda et al., 1977a). Comparison of glandular proliferation and carcinoembryonic antigen staining in hepatolithiasis with and without cholangiocarcinoma led Nakanuma and associates to speculate that the atypical glandular proliferation (carcinoembryonic antigen positive) was a precursor to overt carcinoma.

The association of primary sclerosing cholangitis, ulcerative colitis, and chronic biliary parasitic infestation with the development of cholangiocarcinoma suggests that chronic inflammation and glandular regeneration may be precursors to carcinoma (Morowitz et al.). In a review of the literature in 1974, Ritchie and associates recorded that the incidence of biliary carcinoma in ulcerative colitis patients was one in 246 and one-third of these tumors occurred within the intrahepatic ducts. These tumors developed in patients with long-standing colonic disease (mean

duration of 5 years, with a range of 0-30 years) and the entire colon was usually affected by colitis. The onset of primary sclerosing cholangitis associated with cholangiocarcinoma often occurs at a younger age (Chapman et al.; Qualman et al.; Wee et al.).

Clonorchis sinesis infestation has been deemed responsible for cholangiocarcinoma development in Hong Kong and accounts for 15 percent of primary hepatic carcinomas (fig. 248) (Hou, 1956). In the series of 200 primary hepatic carcinomas (Hou, 1956), 30 cases of cholangiocarcinoma were reported and 28 of those cases occurred in men. Hou (1965) noted that marked bile duct hyperplasia appeared to be a precursor lesion. Similarities of host regenerative response to fluke infestation in man and nitrosamine induced cholangiocarcinoma in the rat have been described (Flavell). The stages of necrosis, glandular proliferation, and tumor growth have parallels in fluke infestation and chemical carcinogenesis. Others have used hamsters infected with Opisthorchis viverrini with an added chemical carcinogen and noted a pronounced synergistic effect. The importance of fluke infestation in man has such a strong association with cholangiocarcinoma development that Belamaric stated that eradication of endemic clonorchiasis should eliminate endemic intrahepatic cholangiocarcinoma. However, as noted by Okuda and associates (1977a), cholangiocarcinoma is worldwide and occurs without fluke infestation.

Cirrhosis has been associated with cholangiocarcinoma, but upon review of the histologic slides in our series, we reclassified some cholangiocarcinomas as

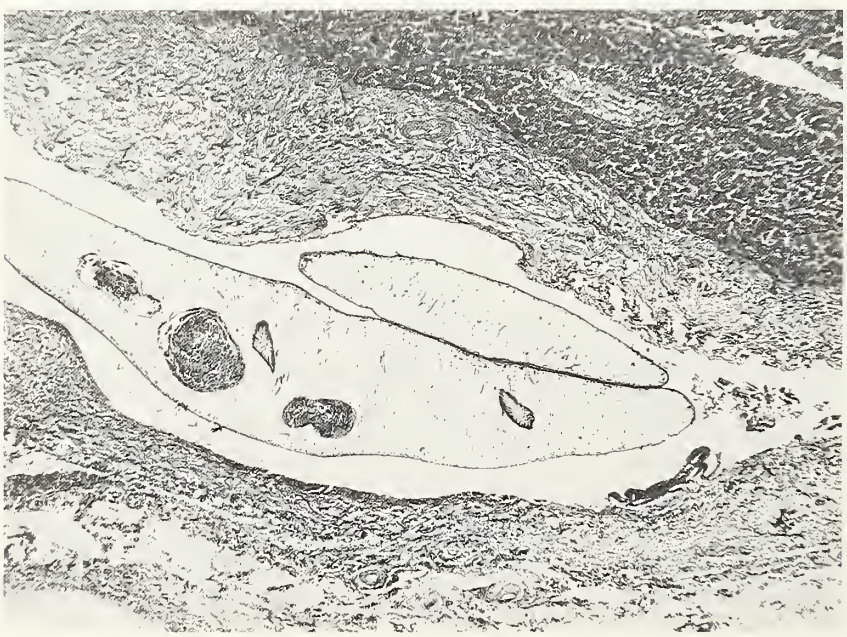


Figure 248
CHOLANGIOCARCINOMA
Clonorchis sinesis is present in a hepatic bile duct of a Chinese man with cholangiocarcinoma (not shown in this field). X40. (Courtesy of Prof. J.B. Gibson, Hong Kong.)

sclerosing hepatic carcinomas because of their histologic appearance and, coincidentally, most of the cirrhotic related "cholangiocarcinomas" were removed. However, in the hilar type, obstruction of the biliary passage produces marked fibrosis, which should not be confused with underlying chronic liver disease.

A few reports of drugs have been associated with cholangiocarcinoma. Intrahepatic cholangiocarcinoma was documented at autopsy in a 47 year old man with refractory anemia who was given anabolic steroid therapy for nearly 2 years (Stromeyer et al., 1979). Methyldopa was implicated in a retrospective study of 82 patients with cholangiocarcinoma (Broden and Bengtsson). However, the strongest etiologic relationship of a drug and cholangiocarcinoma is with Thorotrast. Rubel and Ishak reported six cases and reviewed eight other literature reports of cholangiocarcinoma related to Thorotrast therapy. To be recognized as a Thorotrast-related cholangiocarcinoma, these authors required: (1) a 15 year interval from Thorotrast use and cholangiocarcinoma recognition; (2) intrahepatic cholangiocarcinoma; (3) bile duct dysplasia or transition of benign bile ducts to the cholangiocarcinoma; and (4) an autopsy to exclude an extrahepatic primary adenocarcinoma (Rubel and Ishak). Interestingly, some patients with Thorotrast develop both cholangiocarcinoma and angiosarcoma (Winberg and Ranchod).

Gross. The gross appearance of peripheral cholangiocarcinoma has three patterns: (1) a single large mass; (2) multiple confluent masses (figs. 249, 250), of which one may be larger and thus appear to be the primary focus (fig. 251); or (3) a diffuse form with a tumor in each portal area (pl. IX-A; fig. 252). Unlike

Figure 249
(Figures 249 and 250 are from the same patient)
PERIPHERAL CHOLANGIOCARCINOMA
This peripheral cholangiocarcinoma involves most of this liver so that the site of origin is impossible to determine. There are numerous large cysts in the liver, but none appear to be related to the tumor.

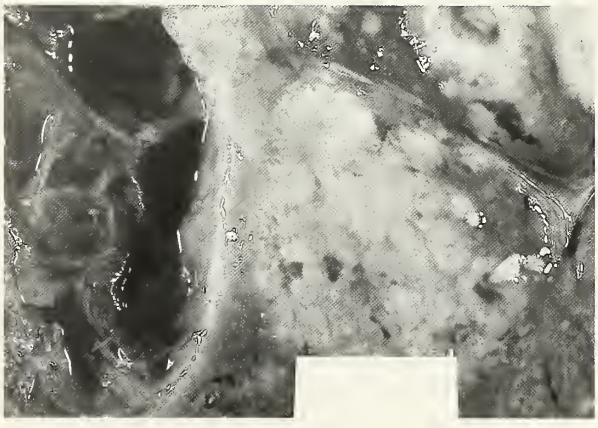


Figure 250
PERIPHERAL CHOLANGIOCARCINOMA
This peripheral cholangiocarcinoma is close to the cyst wall, but does not seem to disturb the epithelium.

Figure 251
CHOLANGIOCARCINOMA
This massive confluent cholangiocarcinoma seems to arise from a major hepatic bile duct, but the tumor growth is so extensive that exact origin is difficult to tell. There are biliary cysts located away from the tumor.

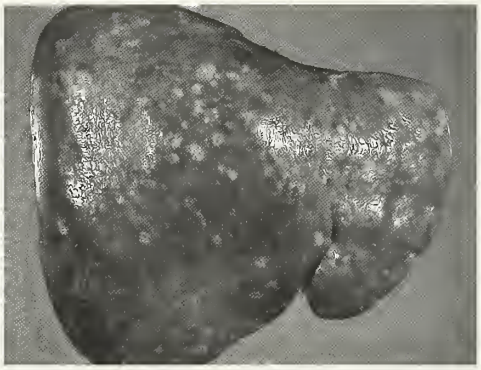


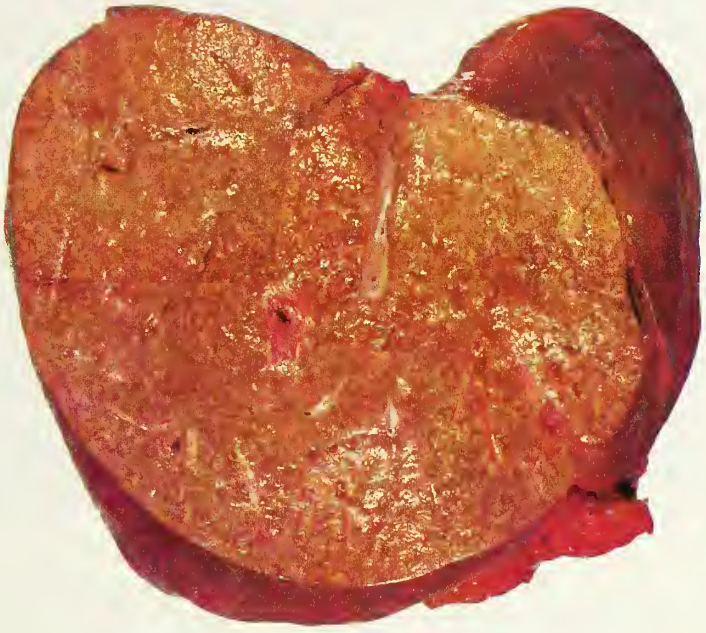
Figure 252
PERIPHERAL CHOLANGIOCARCINOMA
Diffuse multifocal involvement by peripheral cholangiocarcinoma is noted by the many small white nodules.

hepatocellular carcinoma, cholangiocarcinoma is not often noted in a cirrhotic liver, although some pre-existing hepatic ductal (cystic) or fibrotic lesions are common. Numerous sections of dense fibrous tumors arising in the cirrhotic liver are needed in order to properly classify the lesion; usually such tumors are sclerosing hepatic carcinomas. The cut surface of the tumor is typically scar-like with a retracted central area and glistening, fleshy margins. Some nodules may appear to be a keloid because of the dense fibrosis. No peripheral hyperemic zone occurs in cholangiocarcinoma as is noted in metastatic adenocarcinoma.

Microscopic. The most common histologic pattern is the small glandular adenocarcinoma with abundant sclerosis (pl. IX-C). The glands have a small lumen and mucin is produced with a uniform pattern. The glandular epithelium is composed of small cuboidal cells with round nuclei and no nucleoli. Some tumors have predominantly small cells with scanty cytoplasm and little cohesiveness, but abundant sclerosis. Inflammatory reaction within the glandular structures may occur (fig. 253). In a few cases, large glands may be noted with transition to the smaller glands, and papillary growth in a duct is unusual. Variation in growth pattern does occur; one patient with inflammatory bowel disease for 26 years had the usual ductal pattern and other areas of keratinizing squamous carcinoma.

Electron microscopy may help distinguish cholangiocarcinoma from hepatocellular carcinoma. In a cholangiocarcinoma, a basement membrane that often interdigitates surrounds the neoplastic ducts, the nuclei lack nucleoli, there are few cytoplasmic organelles, and microvilli are common (Ordonez and Mackay; Phillips et al.).

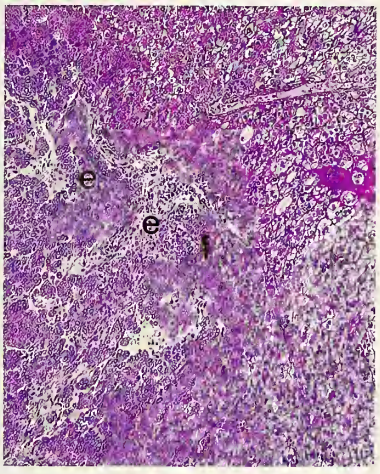
PLATE IX



A. PERIPHERAL CHOLANGIOCARCINOMA

(Plates IX-A and IX-C are from the same patient)

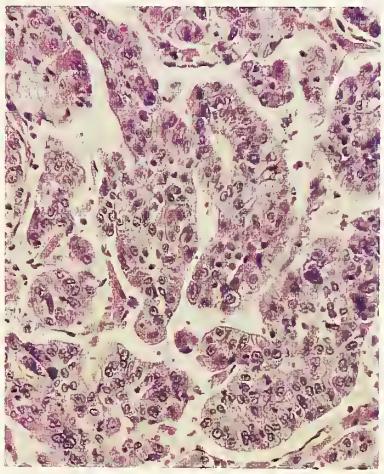
This diffuse peripheral cholangiocarcinoma in a 49 year old alcoholic man has numerous small white granular nodules. (Pl. IV-A from Fascicle 25, First Series.)



B. HEPATOBLASTOMA

(Plate IX-B and figure 245 are from the same patient)

The hepatocellular carcinoma area on the top right merges with the fetal subtype (f) and embryonal carcinoma (e) of the hepatoblastoma. X117. (Courtesy of Dr. Robert Hutter, Livingston, New Jersey.)



C. PERIPHERAL CHOLANGIOCARCINOMA

This papillary adenocarcinoma grade III (peripheral cholangiocarcinoma) has moderate variation in nuclear size and chromatin density. X200. (Pl. IV-B from Fascicle 25, First Series.)

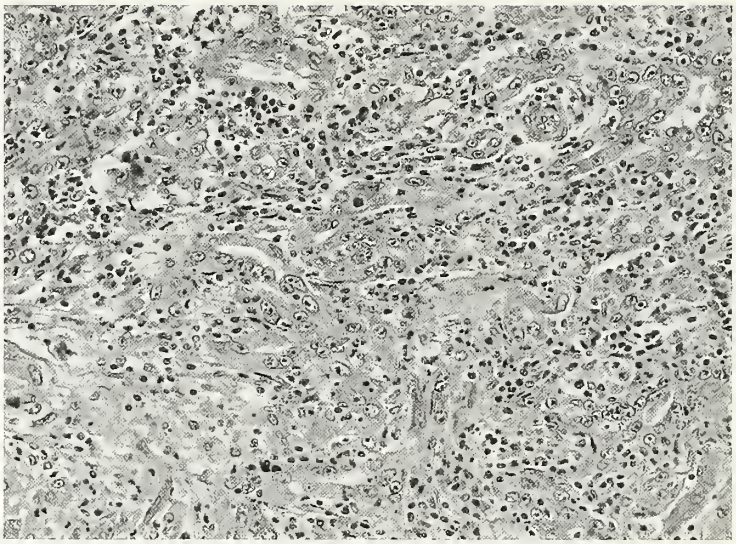


Figure 253
PERIPHERAL CHOLANGIOCARCINOMA
This peripheral cholangiocarcinoma forms fairly large glandular structures and has abundant acute inflammatory reactions surrounding the glands. X100. (Courtesy of the California Tumor Tissue Registry and Dr. David Francis, Torrance, California.)

Differential Diagnosis. The histologic patterns of cholangiocarcinoma resemble several tumors including sclerosing hepatic carcinoma, metastatic adenocarcinoma, cystadenocarcinoma, carcinoid tumors, and epithelioid hemangioendothelioma. Sclerosing hepatic carcinoma may be very difficult to distinguish, but its features include eosinophilic small cells with nucleoli and usually no glandular lumen. Metastatic carcinoma is suspected if large columnar epithelium is present, but many adenocarcinomas resemble cholangiocarcinoma and search for extrahepatic origin is recommended. Mucin production is noted in nearly all cholangiocarcinomas (Weinbren and Mutum). Some hepatocellular carcinomas have such variability in pattern that the transition form of overt hepatocellular carcinoma to cholangiocarcinoma is found. We tend to classify lesions as hepatocellular carcinoma if a large part of the tumor was typical for hepatocellular carcinoma. Therefore, adequate tumor sampling is required.

Carcinoid tumors may have sclerosis and may closely resemble cholangiocarcinoma. Two patients reported by Alpert and associates had histologic features of both cholangiocarcinoma and carcinoid tumors because of the presence of dense core granules detected by electron microscopy. Epithelioid hemangioendothelioma is often confused with cholangiocarcinoma due to the abundant fibrosis separating relatively large epithelioid cells. However, no true neoplastic

ductular structures are formed, although a few trapped bile ducts may persist in the epithelioid hemangioendothelioma.

Variants. Hilar cholangiocarcinoma produces symptoms of extrahepatic bile duct obstruction, although the main tumor is within the hilum of the liver. The major duct component may be a fibrous thickening with spread proximal to the hepatic parenchyma. Although a few reports appeared before 1965, Klatskin collected 13 cases and recognized three major types. The most common type was the small sclerotic scar or nodule that minimally invaded the surrounding tissue but obliterated the duct lumen. Such tumors were often missed at routine exploration and were identified at a second operation. A second type was the intramural tumor that formed a stenotic segment and the third type was the papillary form, which was the least common and minimally invasive. The short papillary growths distinguish it from intraductal papillomatosis (intraductal papillary carcinoma), which has marked distention of the bile ducts by cauliflower masses. In our autopsy series, hilar cholangiocarcinoma is not a small major duct lesion as reported by Klatskin, but is an advanced invasive adenocarcinoma with extensive spread within the liver. The histologic features are similar to the peripheral cholangiocarcinoma and also include prominent fibrosis with small cuboidal epithelium that often has mucin secretion (figs. 254, 255). Recognition of cholangiocarcinoma in the setting of chronic inflammation can be difficult and the presence of glands within the perineural space is very helpful (Qualman et al.). Utilization of special stains for tumor asociated antigens (i.e., carcinoembryonic antigen) and mucin were not helpful in distinguishing benign chronic sclerosing cholangitis from cholangiocarcinoma. Due to the location, symptoms are produced early in the course of hilar cholangiocarcinoma, therefore, patients with the tumor have a better survival rate than patients with peripheral cholangiocarcinoma, which is usually large at the time of diagnosis.

Major duct cholangiocarcinoma may produce a distinctive gross appearance, especially if it arises from either the right or left hepatic bile duct. As the carcinoma grows and obstructs one major bile duct, the more proximal hepatic tissue undergoes atrophy and the opposite hepatic lobe becomes hypertrophied. This pattern of atrophy and hypertrophy is not restricted to carcinoma since benign strictures are known to produce the same change (Czerniak et al.). Of our four patients with major duct cholangiocarcinoma, one has extrahepatic choledochal cyst and Caroli's disease, and two have multiple simple biliary cysts and carcinoma (pl. X-A; figs. 256-259). As a major duct cholangiocarcinoma tumor continues to grow, it will ultimately infiltrate and the mass will obstruct the opposite major bile duct or common bile duct causing jaundice, which allows clinical recognition of the disease (fig. 260). The histologic patterns include the small glands with cuboidal cells, tall columnar cells, marked sclerotic small glandular tumor similar to peripheral cholangiocarcinoma, and papillary adenocarcinoma (fig. 261).

Intraductal papillomatosis, a rare tumor with approximately eight cases in the English literature (Huguet et al.), of which we have three examples for study, is best considered a low grade adenocarcinoma because the few cases with metastasis and invasion have a benign histologic

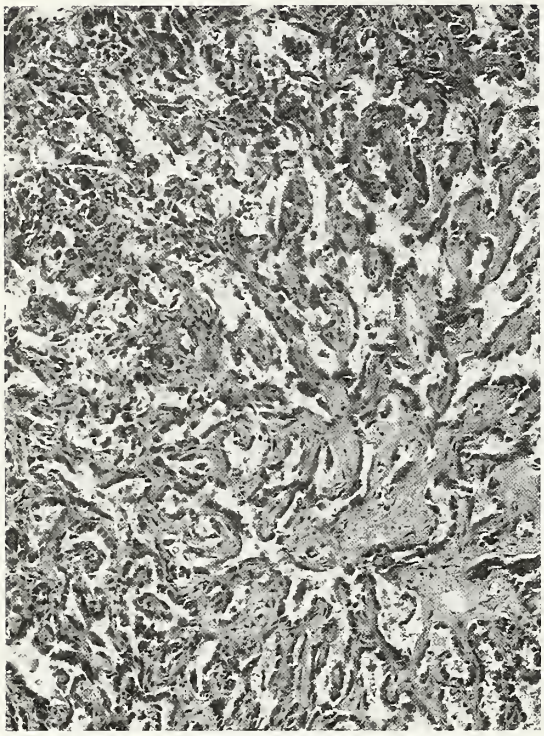


Figure 254
(Figures 254 and 255 are from the same patient)
HILAR CHOLANGIOCARCINOMA
This hilar cholangiocarcinoma arising from the left main intrahepatic bile duct has thick fibrous strands surrounded by cuboidal to polygonal epithelium. X310. (Courtesy of the California Tumor Tissue Registry.)

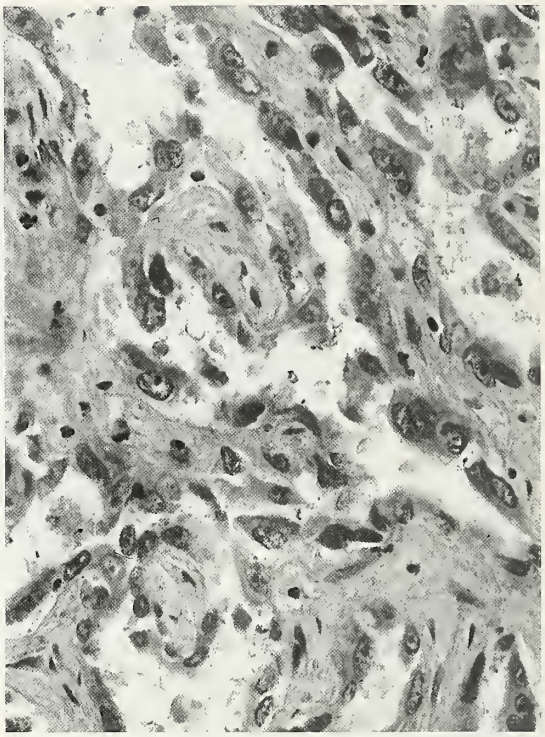


Figure 255
HILAR CHOLANGIOCARCINOMA
This higher magnification of the hilar cholangiocarcinoma in figure 254 shows that the fibrous stroma is lined by cuboidal cells with eosinophilic cytoplasm and the nuclei are small without nucleoli. X1240. (Courtesy of the California Tumor Tissue Registry.)

appearance. Males predominate and the usual age range is 45 to 66 years. Ulcerative colitis and Caroli's disease have also been associated with this unusual variant (Neumann et al.; Payan et al.). These intraductal tumors may be a solitary, sessile, papillary mass, but are usually multiple and involve both intrahepatic and extrahepatic bile ducts and even the gallbladder (Cattell et al.; Eiss et al.; Madden and Smith; Okulski et al.). Histologic examination reveals benign features with cuboidal to columnar epithelium on thin fibrous stalks which form large cauliflower-like papillomata (figs. 262-264). Nuclear atypia and mitoses are rare and invasion is absent, but in one of our three cases, periportal lymph node metastasis was present. The clinical duration of symptoms is often short (months), but the patients have a prolonged survival rate after surgical excision or curettage of fragments (fig. 265); a 4 and 5 year survival rate was reported by Madden and Smith. Death is caused by sepsis and not by the spread of the tumor.

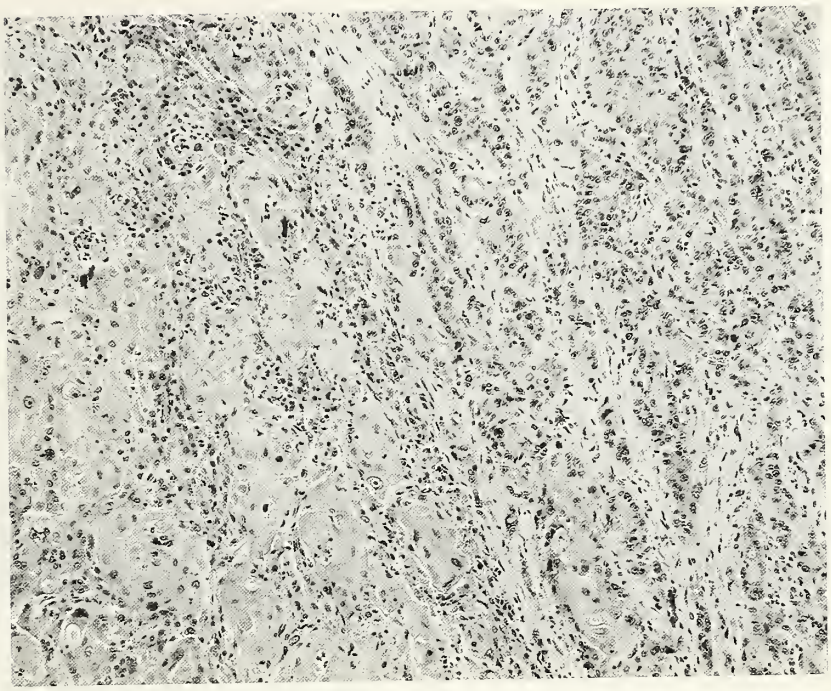


Figure 256
MAJOR DUCT
CHOLANGIOCARCINOMA
This major duct cholangiocarcinoma has mixed squamous carcinoma and adenocarcinoma. X70.

Figure 257
MAJOR DUCT
CHOLANGIOCARCINOMA
These large dilated ducts contain papillary adenocarcinoma (cholangiocarcinoma). X40. (Courtesy of Dr. Milton Hortes, Los Angeles, California.)

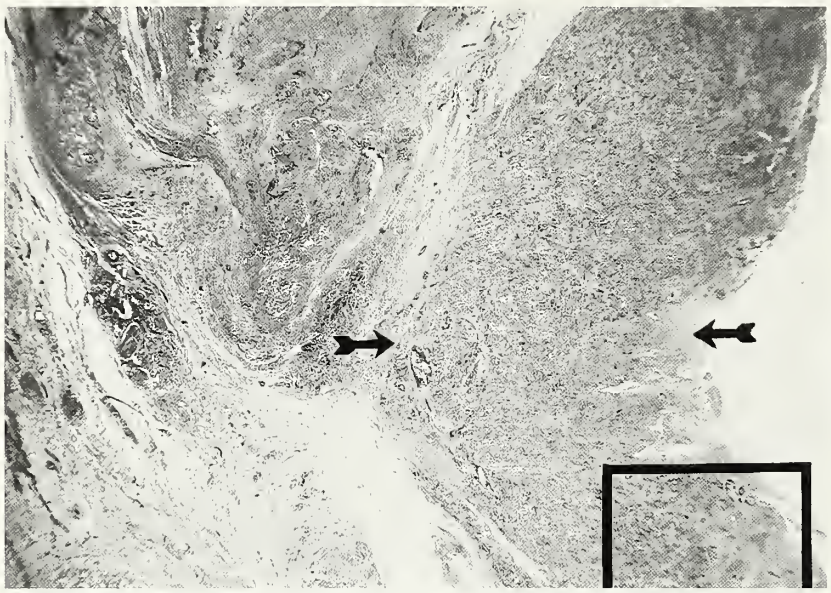


Figure 258
(Figures 258 and 259 and Plate X-A are from the same patient)
MAJOR DUCT CHOLANGIOCARCINOMA
This section of the hilum includes the major right hepatic bile duct and shows the thickened wall with extensive infiltration by cholangiocarcinoma. X10.

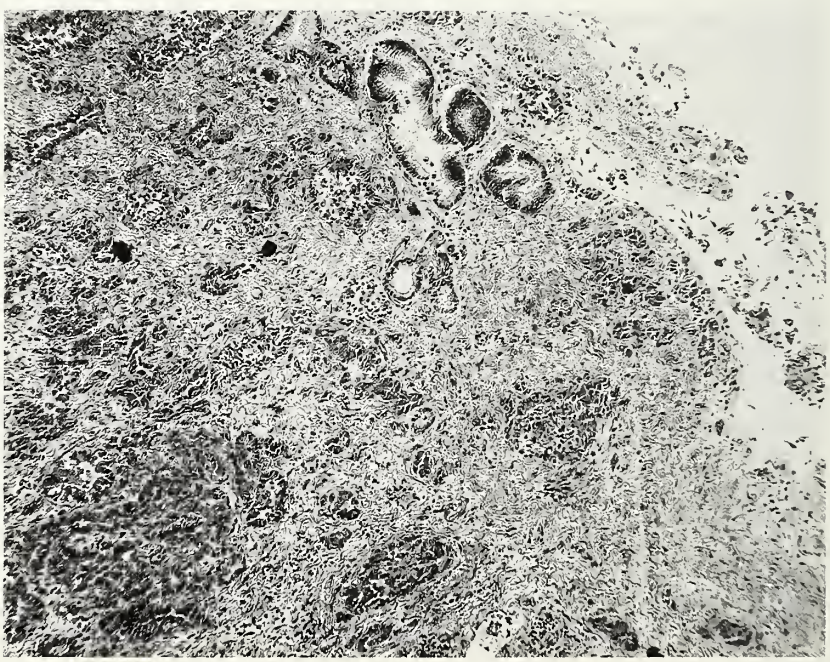


Figure 259
MAJOR DUCT CHOLANGIOCARCINOMA
This higher magnification of the major duct cholangiocarcinoma in figure 258 shows extensive infiltration of the wall by small and irregular malignant glands. X70.

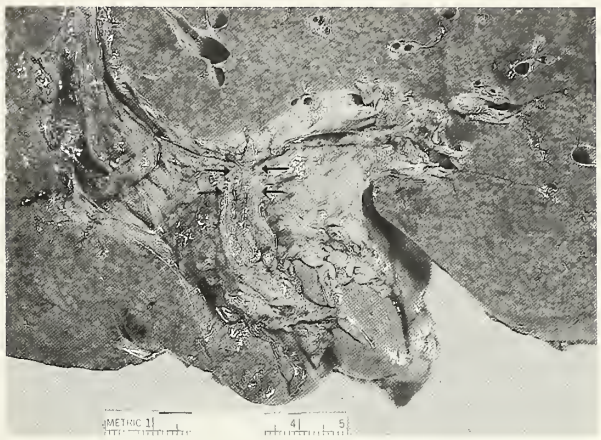


Figure 260
(Figures 260 and 261 are from the same patient)
CHOLANGIOCARCINOMA
This hilar cholangiocarcinoma (arrows) has invaded the duct wall causing obstruction, as illustrated by the bile-stained liver. The tumor is not bulky and very thin.

Figure 261
CHOLANGIOCARCINOMA
This well-differentiated adenocarcinoma with a papillary pattern of bile ducts is growing within a dilated large duct. The underlying bile ducts are benign and have tall columnar epithelium with nuclei at the base of the glands. X117.

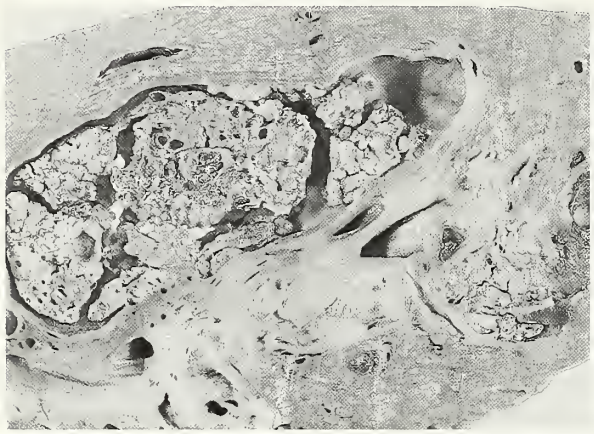


Figure 262
(Figures 262-265 are from the same patient)
INTRADUCTAL PAPILLOMATOSIS
This large papillary tumor seems attached at only one area and the remaining duct epithelium is not proliferative. (Courtesy of Dr. W. Talbert, Long Beach, California.)

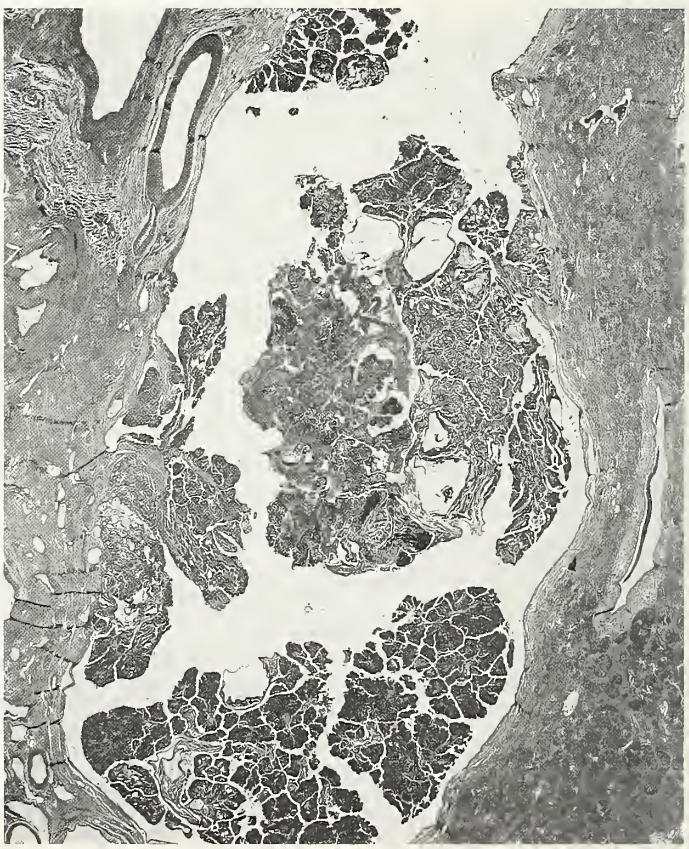


Figure 263
INTRADUCTAL PAPILLOMATOSIS
The papillary growth is well-differentiated with no necrosis in this figure. X2. (Courtesy of Dr. W. Talbert, Long Beach, California.)

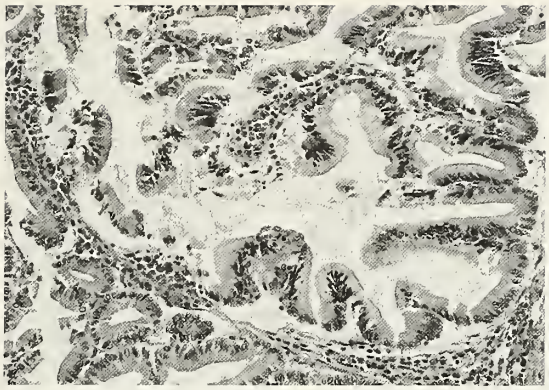


Figure 264
INTRADUCTAL PAPILLOMATOSIS
This intraductal papillary bile duct carcinoma has tall columnar epithelium, no piling up of cells, and all the nuclei are at the base of the glands without mitoses. X420. (Courtesy of Dr. W. Talbert, Long Beach, California.)

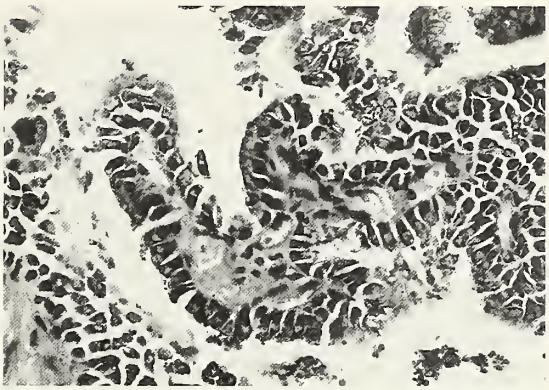


Figure 265
INTRADUCTAL PAPILLOMATOSIS
Curettage of the bile duct produced fragments with moderate cytologic atypia with increased nuclear to cytoplasmic ratio, no mitosis, and no stratification of the columnar epithelium. X840. (Courtesy of Dr. W. Talbert, Long Beach, California.)

Prognosis. Surgical cure of cholangiocarcinoma is unusual because of the failure to detect the tumor in an early stage, but in those patients with a small lesion or intraductal lesion, surgical excision or bypass may result in prolonged survival. The survival rate of unresected cholangiocarcinoma is lower than that of hepatocellular carcinoma. In the Japanese series, although there was a survivor at 77 months, there was only a 3 percent survival at 3 years (Okuda and the Liver Cancer Study Group of Japan). Metastatic spread of peripheral cholangiocarcinoma differs from that of hepatocellular carcinoma (see Table 11) and occurs more often than in hilar cholangiocarcinoma (Okuda and the Liver Cancer Study Group of Japan). No metastases were noted in 23 percent of the tumors, 50 percent had spread to periportal lymph nodes, and the lungs contained cholangiocarcinoma in 43 percent. Serosal spread by cholangiocarcinoma was more common than in hepatocellular carcinoma (23 percent) and bone metastasis occurred in 17 percent. Unusual metastatic sites include the thyroid gland, ovary, skin, and myocardium.

Hepatic failure from obstructive jaundice and debilitation accounted for 60 percent of the deaths in the large series by Okuda and associates (1977a). Hepatic abscess and biliary sepsis are also common. Overall survival was 6.5 months, with the range from 1 to 44.5 months. Hepatic resections prolonged survival in many of the Japanese patients, with several patients doing well 2 to 4 years after surgery. Nine of 11 patients had major hepatic resection (Kawarada and Mizumoto).

CHOLANGIOLOCELLULAR CARCINOMA

Steiner and Higginson introduced the term cholangiolocellular carcinoma in 1957 to describe a rare histologic form of primary hepatic carcinoma that resembled the cholangiole, and therefore was similar to both cholangiocarcinomas and hepatocellular carcinomas. The tumor is composed of small, regular, glandular structures that often enlarge to broader sheets of cuboidal cells with oval nuclei. Trabeculae are not formed, although the cells are larger than the usual cholangiocarcinoma, and sometimes nucleoli are noted. Similar areas of cholangiolocellular carcinoma may be found within numerous sections of either hepatocellular carcinoma or cholangiocarcinoma. This category applies if the majority of the tumor has compatible histologic features. We have only two examples of cholangiolocellular carcinoma in our autopsy series (figs. 266, 267). The clinical course has not been studied in detail due to the lack of uniform criteria and the rarity of the tumor.

CARCINOMA ARISING IN CYSTS

Simple hepatic cysts are rarely the site of malignant change and approximately one-half are squamous carcinoma and the remainder are adenocarcinoma. With extensive growth of the carcinoma, the cyst origin may be obscured, and thus some of the reported cases are likely hepatobiliary cystadenocarcinoma. We have one giant cell carcinoma originating from a large cyst in an autopsy patient in our USC Liver Unit series. However, we believe that many cystadenocarcinomas are derived from hepatobiliary cystadenomas because we have several examples of long-term follow-up indicating the conversion of a benign cystadenoma to a malignant tumor (Rossi et al.).

Hepatic Cystadenocarcinoma

SYNONYMS AND RELATED TERMS: Hepatobiliary cystadenocarcinoma.

Definition. Hepatobiliary cystadenocarcinoma is a malignant tumor and is usually a papillary adenocarcinoma that has developed in a hepatobiliary cystadenoma. Traceability to benign cystadenoma is present in over one-half of the hepatobiliary cystadenocarcinomas.

Incidence. Hepatobiliary cystadenocarcinoma is relatively rare and is responsible for 20 to 40 percent of the reported series of hepatobiliary cystic tumors (Ishak et al.; Wheeler and Edmondson). It is likely that there are less than 50 reported cases. Approximately 15 percent of choledochal cysts develop carcinoma (Voyles et al.).

Clinical. The incidence in males and females appears equal and most patients are 40 to 65 years old. There is a documented association between advancing age and carcinoma in choledochal cysts. Clinical symptoms are abdominal pain and mass, and a few patients have jaundice (usually if related to choledochal cyst).

Pathology. The cysts are usually multilocular and large, with a range of 5 to 14 cm (Ishak et al.). A large papillary mass may occur as well as solid areas of gray-white tumor in a thickened wall. The cyst fluid is bloody in one-third of the cases. Microscopic sections reveal a variety of epithelium including columnar, stratified cuboidal, and squamous epithelium (figs. 268-270). In most cysts, transition of benign simple epithelium to dysplastic cells to carcinoma can be noted (Moore et al.,

Figure 266
(Figures 266 and 267
are from the same patient)
CHOLANGIOLOCELLULAR
CARCINOMA
This cholangiolocellular carcinoma has small cuboidal cells with eosinophilic cytoplasm that form small ductular structures that may also be elongated glands. There is also a moderate degree of fibrosis. X70.

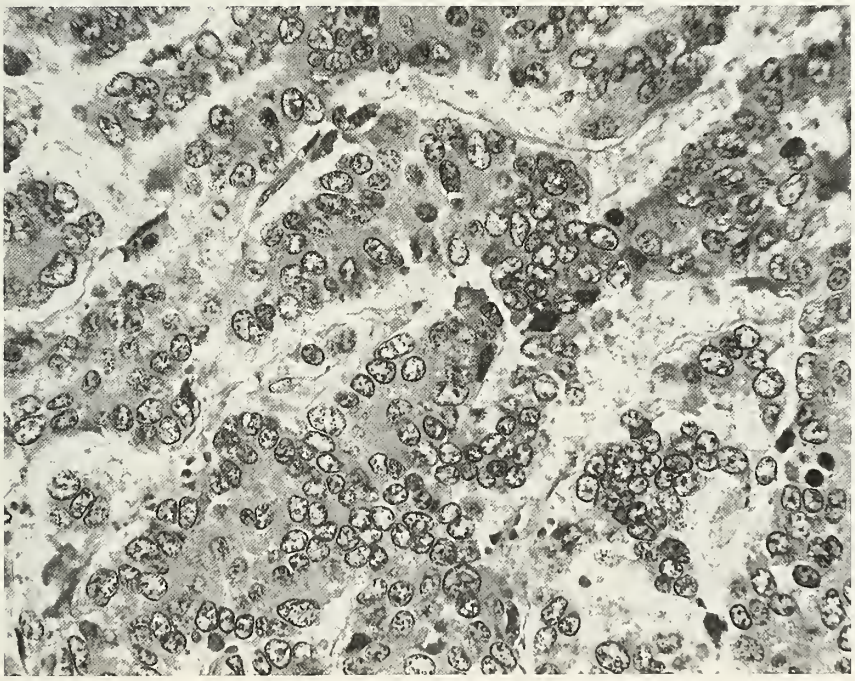


Figure 267
CHOLANGIOLOCELLULAR
CARCINOMA
This higher magnification of the cholangiolocellular carcinoma in figure 266 shows a cord-like arrangement. Canaliculi are hard to find, but occasionally are noted. X585.

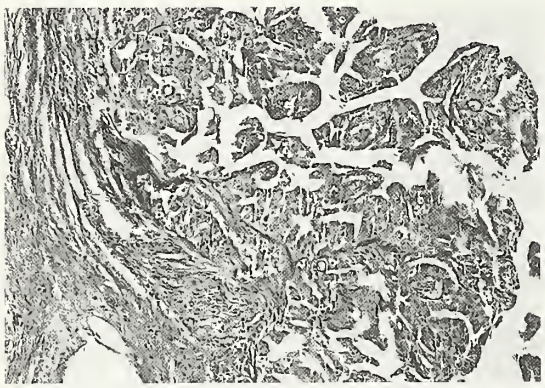


Figure 268
(Figures 268 and 269 are from the same patient)
CYSTADENOCARCINOMA
This cystadenocarcinoma has papillary fronds of stratified cuboidal epithelium with eosinophilic cytoplasm. Mitoses are not common and there is no invasion of the fibrous wall by the adenocarcinoma. X420. (Courtesy of Dr. Morris H. Lukens, Deer Park, California.)

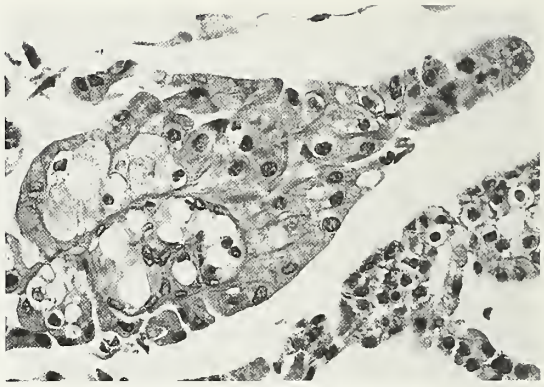


Figure 269
CYSTADENOCARCINOMA
A higher magnification of the cystadenocarcinoma in figure 268 shows multilayered eosinophilic cells from the tip of a papillary adenocarcinoma frond. X840. (Courtesy of Dr. Morris H. Lukens, Deer Park, California.)

1984; Woods). The papillary fronds are multilayered cuboidal epithelium that has eosinophilic cytoplasm (figs. 268, 269). Pseudosarcomatous cystadenocarcinoma has been reported and the immunoperoxidase indicates the spindle cell stroma beneath the poorly differentiated carcinoma stains for keratin, and thus supports the interpretation of spindle cell metaplasia of a carcinoma (fig. 271) (Unger et al.).

Differential Diagnosis. Benign hepatic cysts may occur in a liver with cholangiocarcinoma, yet no direct connection can be identified between the cysts and the carcinoma. Thus, even though the gross appearance may suggest cystadenocarcinoma, there may not be any traceability of the cyst lining to malignant change and to the cholangiocarcinoma. Therefore, hepatic cysts must be carefully studied to relate any carcinoma to the cyst wall. The prognosis of cholangiocarcinoma with hepatic cysts is poor and the treatment is different since hepatobiliary cystadenocarcinoma is more often resected than cholangiocarcinoma (Imamura et al.).

SQUAMOUS CELL CARCINOMA

SYNONYMS AND RELATED TERMS: Epidermoid carcinoma; adenoacanthoma; mucoepidermoid carcinoma.

Definition. Squamous cell carcinoma of the liver is a primary hepatic carcinoma with squamous differentiation in the majority of the tumor. Squamous features include keratin formation, glassy eosinophilic cytoplasm, and intercellular bridges.

Incidence. Squamous cell carcinoma of the liver is rare and in our files we have five cases, of which two are in the large autopsy series. There are case reports in the literature.

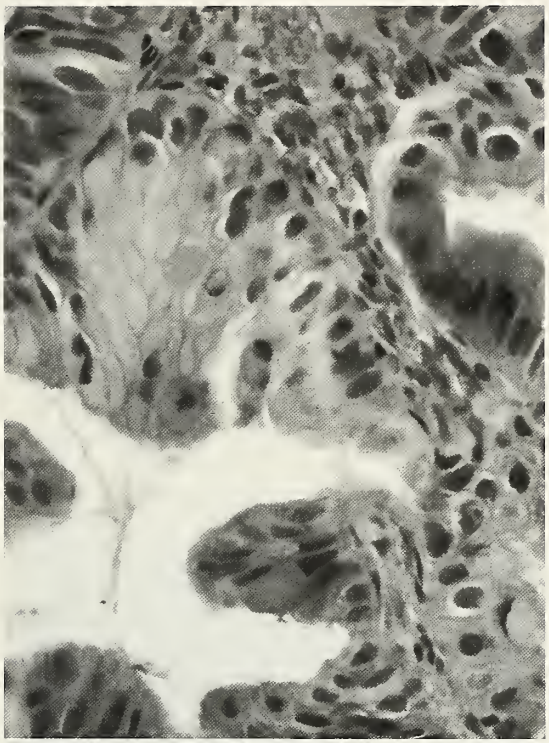


Figure 270
CYSTADENOCARCINOMA
Marked eosinophilia is noted in the tall columnar epithelium from a cystadenocarcinoma. X1240.

Figure 271
CYSTADENOCARCINOMA
This hepatobiliary cystadenocarcinoma has little surface cuboidal epithelium, but the underlying basophilic cells are keratin positive and are poorly differentiated adenocarcinoma with a spindle cell stroma, which is also keratin positive by immunoperoxidase technic. There are multiple small cysts included in this field. X620. (Courtesy of Dr. Swan Thung, New York, New York.)

Clinical. Most squamous cell carcinomas arise in chronic conditions predisposing to cholangiocarcinoma such as long-standing inflammatory bowel disease, multiple hepatic cysts including Caroli's disease (Bloustein) or chronic hepatolithiasis (Song et al.). In our review of 10 cases (our own and from the literature), five tumors derived from hepatic cysts and five from biliary ducts. Males predominated (9 of 10) and the age range was 26 to 76 years. One patient had hypercalcemia.

Pathogenesis. Because the majority of the tumors arise in chronic inflammatory biliary conditions or hepatic cysts, it is likely that the tumor is derived from squamous metaplasia secondary to chronic inflammation in a biliary lined cyst or duct.

Pathology. The gross appearance of squamous cell carcinoma may be either a large cystic mass with squamous carcinoma in the wall or multiple nodules (1-10 cm) spread diffusely within the liver. The cut surface may be granular and gray-

white to green-brown with central necrosis of the larger nodules. The histologic features are similar to squamous cell carcinoma in other organs. The well-differentiated tumor has squamous pearl formation (figs. 272, 273). Poorly differentiated areas have small cells, often with necrosis, and cannot be recognized as squamous cell carcinoma unless there is continuity with the better differentiated areas of the tumor. Pianzola and Drut reported mucous producing cells in one squamous cell carcinoma .

Differential Diagnosis. Metastatic squamous cell carcinoma is far more common than primary tumor. The association of chronic inflammatory condition and hepatolithiasis supports the diagnosis of primary tumor, but traceability of the malignant squamous cell carcinoma to metaplastic benign squamous epithelium is diagnostic of the origin of the tumor.

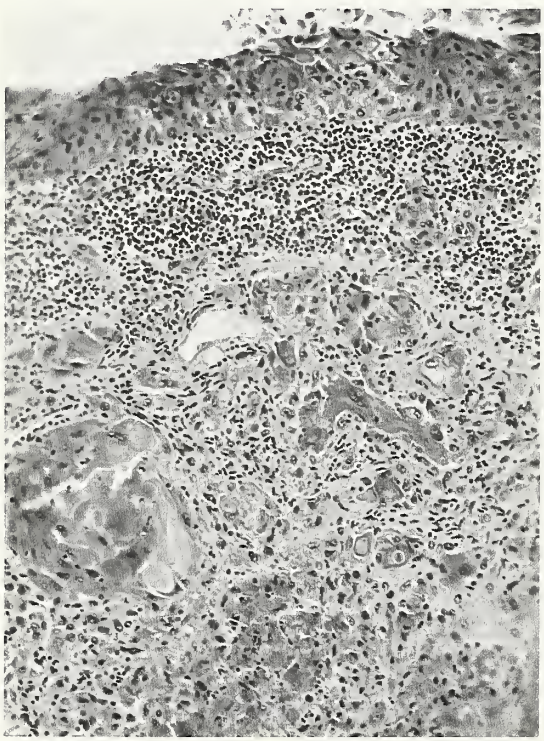


Figure 272
(Figures 272 and 273 are from the same patient)
SQUAMOUS CELL CARCINOMA
The cyst wall has squamous metaplasia and within the underlying stroma, there is invasive squamous carcinoma composed of polygonal eosinophilic cells with central nuclei. (Fig. 100 from Fascicle 25, First Series.)

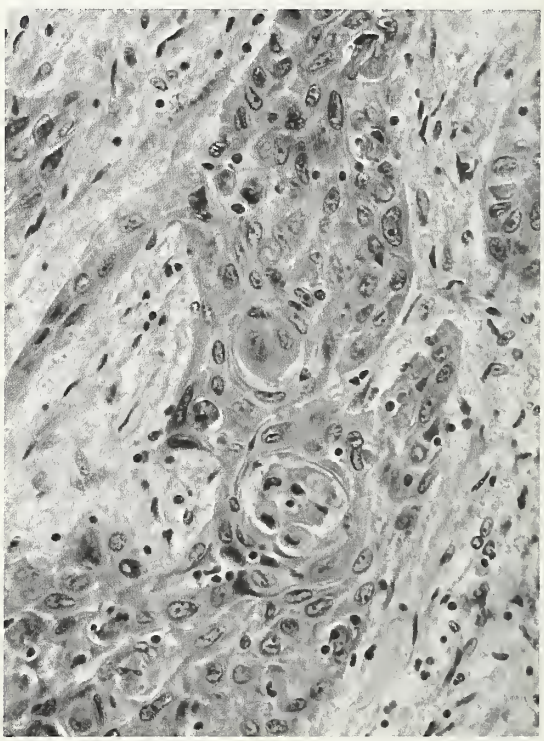


Figure 273
SQUAMOUS CELL CARCINOMA
A higher magnification of figure 272 shows early squamous pearl formation in the center of the cluster of squamous carcinoma. The polygonal cells become more elongated and the nuclei shrink with dark chromatin as the squamous pearl "matures." Nucleoli are common in many cells. (Fig. 101 from Fascicle 25, First Series.)

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PRIMARY MALIGNANT MESENCHYMAL TUMORS

Sarcoma arising in the liver is rare and the most common type, angiosarcoma, is derived from vascular cells. All the mesenchymal elements of the liver have been identified as precursors to malignant tumor and are classified similar to sarcomas found elsewhere in the body. Unfortunately, accurate classification is often difficult as the bland spindle cell tumors frequently lack identifying characteristics and subtle differences lead to separation into such groups as fibrous mesothelioma, fibrosarcoma, and leiomyosarcoma. In many tumors, there is considerable variation in different areas and mitoses are rare despite moderate cellularity. By application of electron microscopy and immunoperoxidase procedures, some additional criteria are identified, but even with these technics using currently available antibodies, the majority of bland spindle cell tumors are difficult to properly classify.

Adequate sampling of these large tumors is essential in order to identify the predominant component and for subsequent classification according to this component. If a mixture of numerous sarcoma variants is present with multiple sections from each variant, the term malignant mesenchymoma is appropriate. However, it is common for some areas of many sarcomas to contain small foci of other sarcomatous differentiation. The term malignant mesenchymoma is rarely applied because a predominant pattern is usually identified after numerous sections. A single case of dedifferentiated liposarcoma of the liver has been reported with evidence of pleomorphic sarcoma and well-differentiated liposarcoma (Kim et al.).

ANGIOSARCOMA

SYNONYMS AND RELATED TERMS: Angioblastic sarcoma; angioplastic sarcoma; angiosarcoma endothelioblastoma; Kupffer cell sarcoma; malignant hemangioendothelioma.

Definition. Hepatic angiosarcoma, a malignant tumor derived from the endothelial lining cell, occurs primarily in adult men, is associated with a variety of chemical agents and radiation exposure, and has a poor prognosis.

Incidence. Hepatic angiosarcoma is rare, but is the most common malignant mesenchymal tumor of the liver. Approximately 25 cases occur each year in the United States. One hepatic angiosarcoma was noted for every 30 hepatocellular carcinomas in the 1951-1973 autopsy series from the Cook County Hospital in Chicago (Ishak). The incidence at autopsy is 6 per 100,000, and nearly 200 patients had been reported by 1981 (Anonymous).

Clinical. The clinical features of hepatic angiosarcoma are similar regardless of underlying associated conditions. The male:female ratio is 3:1, and the average age is 53 years (Locker et al.). In our review material of 16 patients with hepatic angiosarcoma, only two patients were females. Childhood angiosarcoma is rare, with less than 12 patients reported by 1984 (figs. 102, 103) (Falk et al.; Noronha and Gonzalez-Crussi). Hepatomegaly is common in 50 percent of the cases; ascites occurs in 25 percent of the cases, and jaundice is also reported in 25 percent of the cases. Thrombocytopenia occurs in 50 percent of the cases and rupture and acute hemoperitoneum occurs in 15 percent (Ishak). Normal serum values for

α-fetoprotein and carcinoembryonic antigen are noted and there is no association with the hepatitis B virus.

Filling defects in the liver are noted in 70 percent of the cases, therefore, arteriography is helpful in diagnosis and demonstrates the extent of the lesion. Liver biopsy at operation is far safer and more accurate than blind needle biopsy (Locker et al.).

Pathogenesis. In the large review by Locker and associates, 40 percent of 103 cases were related to one of several factors including: Thorotrast (15 cases); vinyl chloride (22 cases); arsenical ingestion (2 cases); radium implant (1 case); and hemochromatosis (3 cases). Thorotrast-induced hepatic angiosarcoma has been recognized for several decades and accounts for 25 percent of the Thorotrast-induced tumors (Kojiro et al.). The Thorotrast latency period is 20 to 36 years and the tumor occurs primarily in men. Vinyl chloride was widely used in the chemical industry for 40 years and is known to be associated with hepatic angiosarcoma. Exposure of mice to vinyl chloride inhalation for 6 to 12 months produces a spectrum of hepatic changes including hepatic angiosarcoma (Hong et al.). Cirrhosis has been considered a possible factor and in our material, two patients had alcoholic cirrhosis. Of our 16 patients, one had Thorotrast exposure, one had arsenical ingestion of Fowler's solution (for psoriasis), and one also had hemochromatosis. Therefore, one-third of our cases have recognized underlying factors.

The evolution of the lesion in vinyl chloride workers apparently requires many years, and liver biopsies of vinyl chloride exposed patients reveal hepatic fibrosis, sinusoidal cell hyperplasia, and hepatocytic nodular regenerative hyperplasia (Creech and Johnson; Mark et al.; Popper et al.). Some patients exposed to vinyl chloride demonstrate portal hypertension prior to the onset of malignant tumor.

Gross. Hepatic angiosarcoma appears in a variety of patterns and the tumor foci may be very small and diffuse, or large and hemorrhagic. Kojiro and associates described four patterns: (1) diffuse micronodular, found in 8 of 18 patients (fig. 274); (2) diffuse multinodular, found in 7 of 18 patients (fig. 275); (3) massive, found in 2 of 18 patients; and (4) mixed, found in 1 of 18 patients. The nodules bulge from Glisson's capsule and may rupture and bleed. The cut section reveals round nodules with irregular margins and solid gray-white areas, as well as large cavernous areas which may have thrombosis and subsequent necrosis. The nontumorous liver in patients exposed to Thorotrast, vinyl chloride or arsenicals may have cirrhosis or fibrosis.

Microscopic. Combinations of sinusoidal, cavernous, nodulopapillary, and solid spindle cell growth patterns are noted (Delorme). The earliest recognizable feature is hypertrophic sinusoidal lining cells with hyperchromatic nuclei. These changes are focal, may involve only a lobule, and may be noted in lobules distant from the major tumor. A needle biopsy of such an area is difficult to recognize as hepatic angiosarcoma since the transition of overt hepatic angiosarcoma to endothelial hyperplasia is a spectrum. Occasionally, diffuse sinusoidal endothelial hyperplasia occurs in most of the liver even though the hepatic angiosarcoma is apparently only in one lobe. The endothelial lining cells increase in number, become enlarged, and separate the hepatocytes, producing the sinusoidal pattern

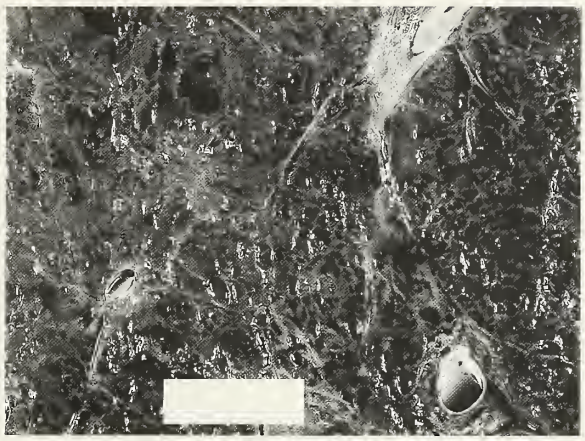


Figure 274
HEPATIC ANGIOSARCOMA

This diffuse micronodular hepatic angiosarcoma has uniform distribution of small round hemorrhagic nodules that are not very apparent on the cut surface, which is hemorrhagic with very small cysts. The 37 year old man had no known toxic exposure. (Courtesy of Dr. Gary Kanel, Downey, California.)

Figure 275
HEPATIC ANGIOSARCOMA

This hepatic angiosarcoma is a diffuse multinodular hemorrhagic tumor involving both lobes of the liver. The liver weight was 7000 g and the large veins were not involved. The 43 year old man had chronic cough, weakness, night sweats, and right chest pain for 10 months. (Fig. 125 from Fascicle 25, First Series.)

(figs. 276, 277). As the sinusoids become dilated, a cavernous pattern is noted (fig. 277). The endothelial cells become more variable in size and shape, have large nuclei, and become multilayered adjacent to atrophic hepatocytes (figs. 278, 279). Collagen production fills some of the sinusoids and replaces the atrophic hepatocytes. Nodulopapillary foci have a mixture of nodular stroma-like areas (spindle cells) and hyperchromatic endothelial malignant cells in papillary clusters (fig. 280). Solid endothelial masses of plump spindle cells may be interspersed with other areas of cavernous change (figs. 102, 103, 281).

Mitotic figures vary greatly in number, and bizarre hyperchromatic and multinucleated cells may be clustered. Solid tumor nodules occur in nearly one-half of the cases and are composed of elongated spindle cells with scattered slit-like spaces that do not have obvious malignant endothelial cells. This solid pattern resembles fibrosarcoma (fig. 281). Phagocytosis of tumor cells (cannibalism) may be striking.

Invasion of the large veins is variable and involvement of the hepatic veins is more common than the portal vein (fig. 282). In one patient with alcoholic cirrhosis, intravenous growth was dramatic, suggesting that the tumor may have originated from the major hepatic vein.

Prognosis. Survival with hepatic angiosarcoma is short, with a mean life expectancy of 6 months; 50 percent of the patients succumb to hepatic failure. Extrahepatic spread is most commonly noted in the spleen. Pulmonary metastasis occurs in small branches of the pulmonary artery and alveolar hemorrhage may result.

Treatment of hepatic angiosarcoma is empirical and few patients have limited tumor at diagnosis to allow surgical resection. Extensive preoperative evaluation usually reveals the tumor in both lobes, and thus surgical cure is not feasible. The longest reported survivor (7 years) received radiation therapy (Alrenga, 1975a). A variety of chemotherapeutic drugs have been tried with limited results and insufficient data is available to determine the most effective regime (Locker et al.).

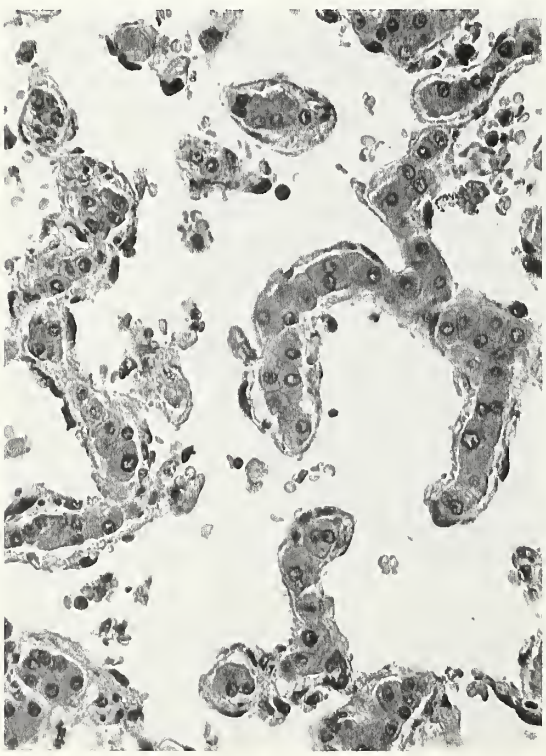


Figure 276
HEPATIC ANGIOSARCOMA
In this hepatic angiosarcoma, the sinusoids are markedly dilated and lined by plump, large, malignant endothelial cells with irregular nuclei and dark chromatin. Irregular nuclear projections extend into the sinusoidal lumen. The hepatocytes are atrophic and are smaller than normal cells. X260. (Fig. 131 from Fascicle 25, First Series.)

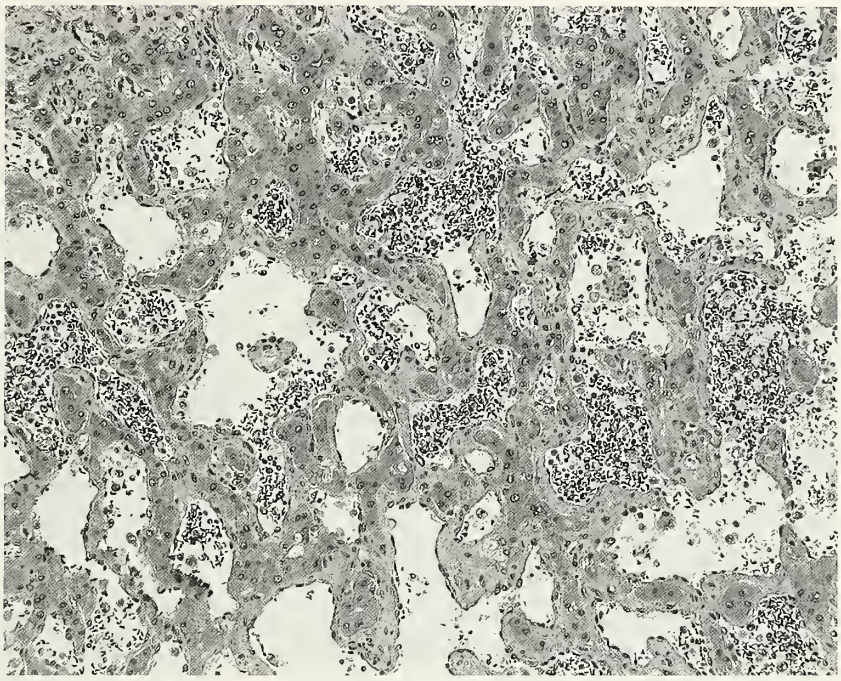


Figure 277
(Figures 277 and 278
are from the same patient)
HEPATIC ANGIOSARCOMA
There is diffuse growth of hepatic angiosarcoma throughout the sinusoids and covering the hepatic cords. At low magnification, the uniform diffuse growth suggests a lacy network with stroma, but figure 278 confirms that the malignant endothelial cells are supported by the hepatic cords. X70. (Courtesy of Dr. Gary Kanel, Downey, California.)

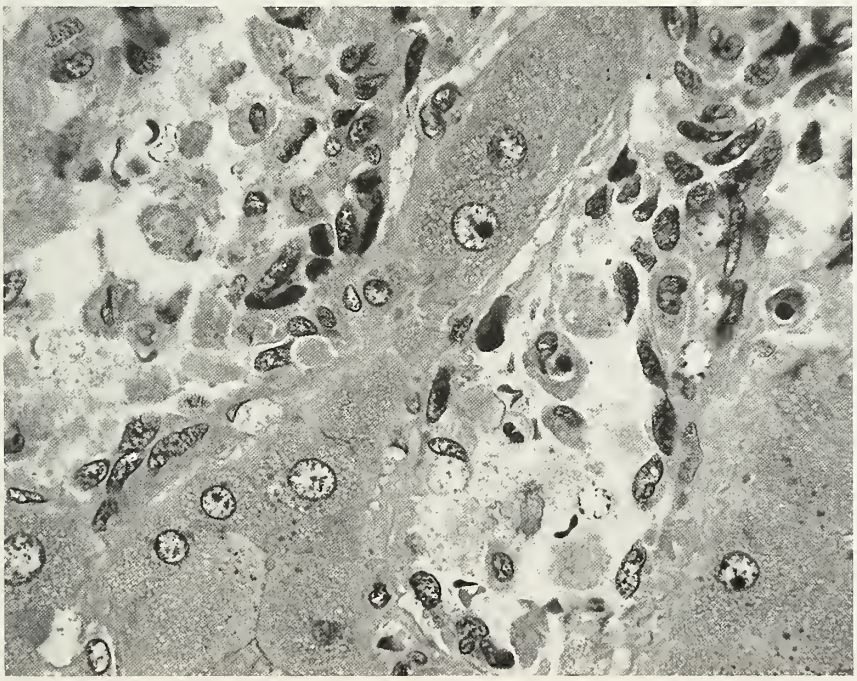


Figure 278
HEPATIC ANGIOSARCOMA
The endothelial lining of this diffuse hepatic angiosarcoma is composed of multiple layers of hyperchromatic spindle cells with little cytoplasm and no nucleoli. The nuclei have many bizarre shapes. X585. (Courtesy of Dr. Gary Kanel, Downey, California.)

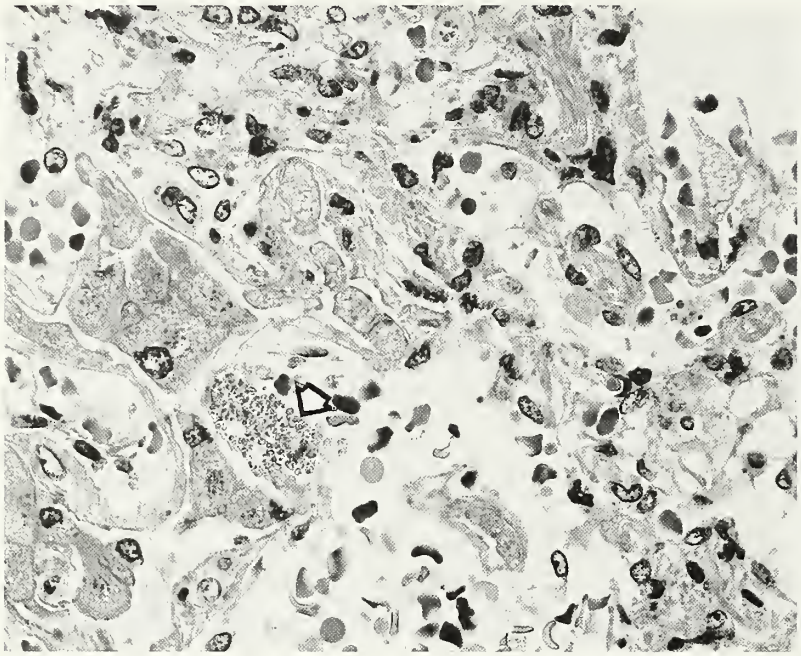


Figure 279
HEPATIC ANGIOSARCOMA
Malignant endothelial cells (with irregular elongated nuclei and scant cytoplasm) and macrophages containing brown granular pigment typical of Thorotrast (arrow) are prominent in this hepatic angiosarcoma. The 61 year old man received Thorotrast in the 1930s and died in 1978 of carcinosarcoma (combined angiosarcoma and cholangiocarcinoma). X117. (Courtesy of Dr. Gerald Bordin, La Jolla, California.)

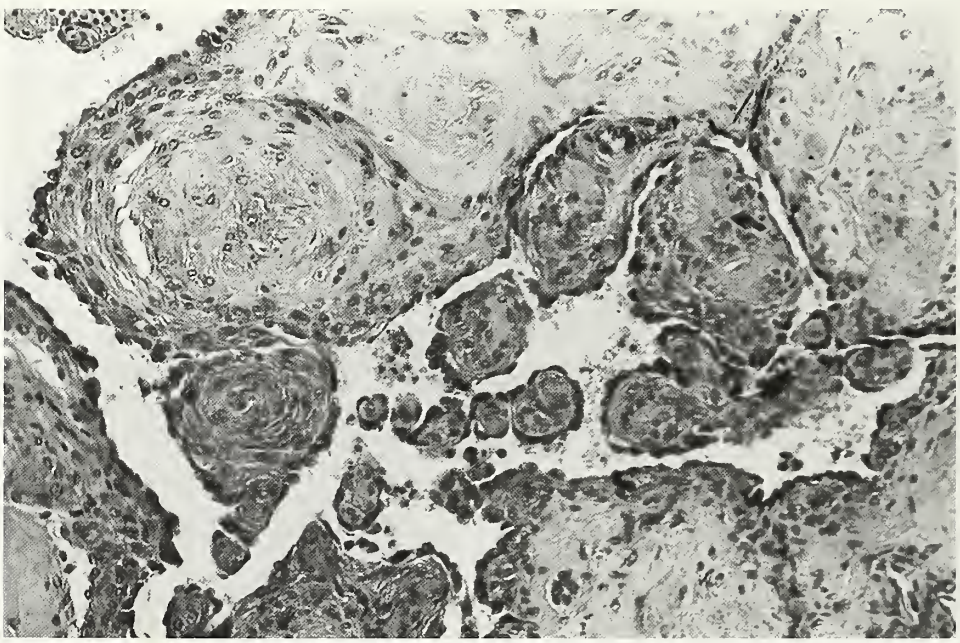


Figure 280
HEPATIC ANGIOSARCOMA
This nodulopapillary form of hepatic angiosarcoma with underlying fibrous stroma occurred in a vinyl chloride worker. X250. (Courtesy of Dr. F. Delorme, Quebec, Canada.)

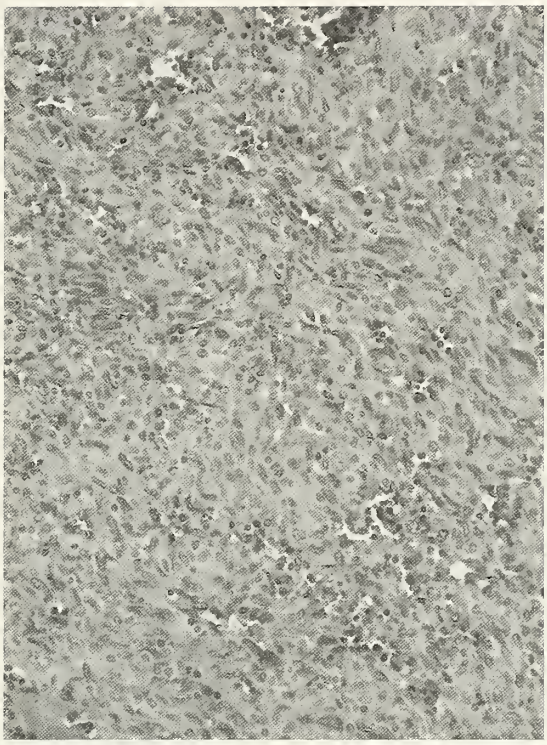


Figure 281
HEPATIC ANGIOSARCOMA
This hepatic angiosarcoma has solid areas composed of relatively plump cells with spindle-shaped cytoplasm and rounded nuclei. Numerous vascular channels are absent. X620. (Courtesy of Dr. Robert Woods, Los Angeles, California.)

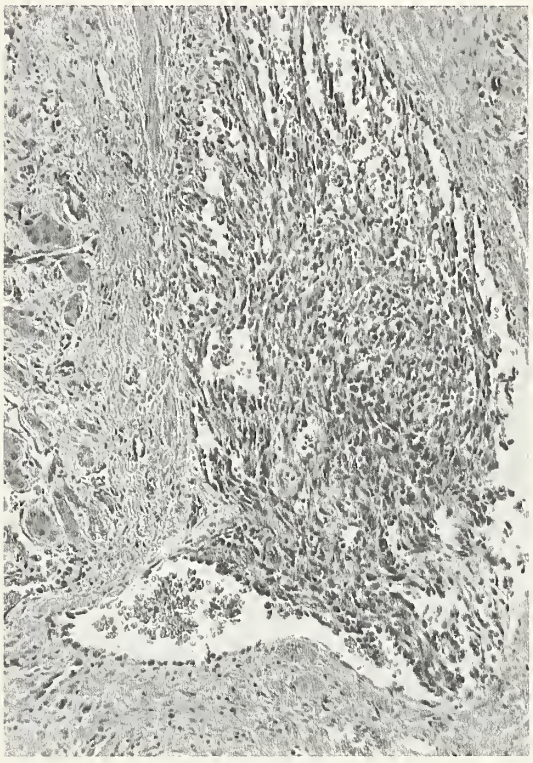


Figure 282
HEPATIC ANGIOSARCOMA
This angiosarcoma has extended into a major hepatic vein and is attached to the vein wall. The tumor is a relatively solid mass of spindle cells with numerous small vascular slits, and individual cells have scant cytoplasm but large hyperchromatic nuclei. X110. (Fig. 129 from Fascicle 25, First Series.)

Differential Diagnosis. Metastatic angiosarcoma appears histologically identical to a primary hepatic tumor (Ludwig and Hoffman). A small biopsy may be difficult to interpret because several small cell tumors must be considered, of which lymphoma is a primary consideration. Immunoperoxidase staining for Factor VIII is often present, indicative of angiosarcoma (Guarda et al.). Solid areas resemble fibrosarcoma however, and additional sections will reflect the angiomatous neoplasm. Typical enlarged endothelial tumor nuclei with variable nuclear shape occur in hepatic angiosarcoma; fibrosarcoma has more uniform nuclei.

EPITHELIOID HEMANGIOENDOTHELIOMA

SYNONYMS AND RELATED TERMS: Vasoablative endotheliosarcoma; intravascular bronchiolar and alveolar tumor of the lung; pseudocartilaginous sarcoma; mixed tumor; sclerosing endothelial tumor; sclerosing interstitial vascular sarcoma.

The commonly accepted name, epithelioid hemangioendothelioma, does not reflect the often progressive and malignant behavior of the hepatic variant of this tumor first described in soft tissue. Therefore, we recommend the term sarcoma or malignant be added to the name, and prefer the term malignant epithelioid hemangioendothelioma for those tumors of hepatic origin.

Definition. Malignant epithelioid hemangioendothelioma is a slowly growing, malignant tumor composed of epithelioid cells, abundant sclerosis, and myxoid stroma. It arises in soft tissue, lung, and liver, and metastasizes often to the lung and possibly to the liver.

Incidence. Hepatic malignant epithelioid hemangioendothelioma has been reported in series as large as 32 patients as well as in several smaller series (Ishak et al.). We have 21 patients in our series, most of whom are referred cases and are also included in the other published series.

Clinical. There are 20 females and 12 males in the largest reported series of hepatic malignant epithelioid hemangioendothelioma. This female predominance contrasts with the equal sex occurrence of the same tumor arising in soft tissue (Ishak et al.). The age ranges from 19 to 86 years, with the mean age of 50 years. The youngest patient in our series is 3 years old. The majority of patients are evaluated for nonspecific complaints including weight loss, abdominal pain, and fever. Jaundice occurred in 4 of 32 patients and one patient had an acute abdomen due to rupture and bleeding of the tumor. The lesions may be massive at the time of diagnosis and repeated biopsy may be necessary to appreciate the proper diagnosis. Budd-Chiari syndrome may be produced by the massive lesion in a late stage (Clements et al.).

Routine laboratory studies are of little help as the serum alkaline phosphatase is elevated in two-thirds of the cases and the α-fetoprotein is normal. Radiographic studies indicate hepatic mass with focal calcification in 20 percent of the cases. Hypertrophy of the uninvolved remaining lobes may be a diagnostic clue.

Pathogenesis. The endothelial cell is the apparent cell of origin because of the prominent Factor VIII staining reaction. Oral contraceptive use has been associated with this tumor in women by Dean and colleagues, who reported five patients with exposure to the medication for 4 to 7 years. However, most patients have no drug exposure history. The tumor does not arise in the setting of chronic liver disease and no viral etiology has been suggested.

Gross. The external surface may appear retracted and irregular, with the cut surface reflecting dense fibrous scar tissue (pl. X-B). The liver is enlarged and a main mass is usual with separate nodules often involving both lobes. The solitary nodules range from 3 to 11 cm (Ishak et al.).

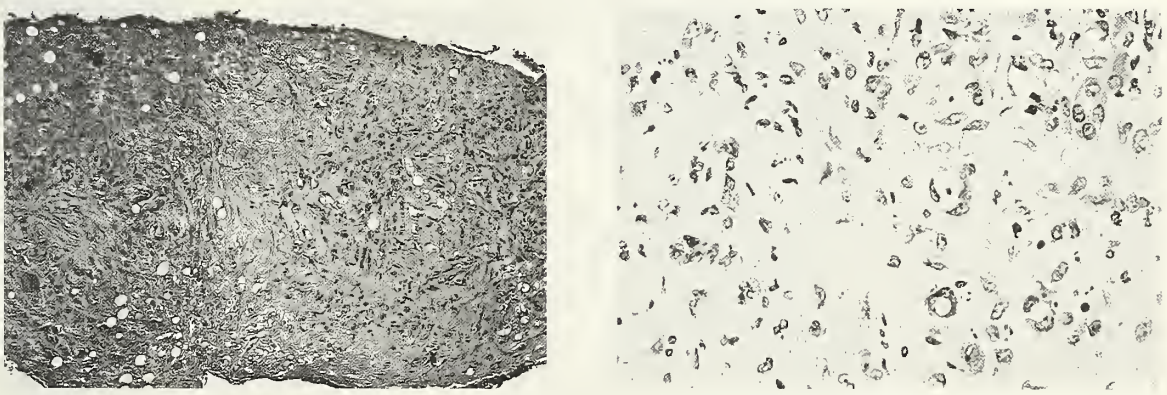
Microscopic. The microscopic pattern of the tumor varies within the same tumor. In the early stages of a small lesion, there are multiple areas of involvement several millimeters in diameter. The centers of these areas are densely fibrotic with remnants of portal areas such as small intact

bile ducts. Within the fibrosis are scattered, elongated cells with vacuolated cytoplasm, called dendritic cells, and dystrophic calcification. At the periphery of the sclerotic mass, plump, pleomorphic, epithelioid cells extend into adjacent sinusoids. These cells have abundant, densely eosinophilic cytoplasm, and often large nuclei and mitoses; these features suggest a highly malignant neoplasm (fig. 283). Many areas have cells that are intermediate forms not readily classified into either of these epithelioid or dendritic forms.

As the sinusoids at the periphery are occluded by the endothelial growth, the adjacent hepatocytes become atrophic and a few remain encased in the fibrous stroma (figs. 284, 285). As the hepatocytes disappear by atrophy, a pseudocartilaginous appearance of the stroma appears. In addition, the major veins become occluded by the tumor cells and the fibrous stroma fills the lumen leaving remnants of the vein wall (fig. 286). Recanalization of the occluded vessel is common. This vascular occlusion may promote degeneration including infarction, necrosis, and hemorrhage of the central areas.

The stromal inflammatory reaction contained predominantly lymphocytes (9/32), neutrophils (20/32), and eosinophils (13/32), whereas angiosarcoma rarely demonstrates such a prominent inflammatory component. The Factor VIII stain by immunoperoxidase confirms the vascular origin and demonstrates positive reaction of the plump epithelioid and dendritic cells, with the strongest staining adjacent to the vacuolization. The nontumor liver is normal in the majority of patients, and there is no relationship to cirrhosis or chronic liver disease.

Electron Microscopy. Neoplastic cells are surrounded by an external lamina and are embedded in collagenous stroma. Cytoplasmic vacuoles are devoid of any



A B

Figure 283
EPITHELIOID HEMANGIOENDOTHELIOMA

A. This malignant epithelioid hemangioendothelioma was noted in a liver biopsy taken 4 years before the patient's death and shows marked sclerosis with scattered individual epithelioid cells adjacent to a nearly normal liver. X45. (Courtesy of Dr. Nathan B. Friedman, Los Angeles, California.) B. The central area of this malignant epithelioid hemangioendothelioma has abundant fibrosis with scattered elongated dendritic cells that are vacuolated. X840.

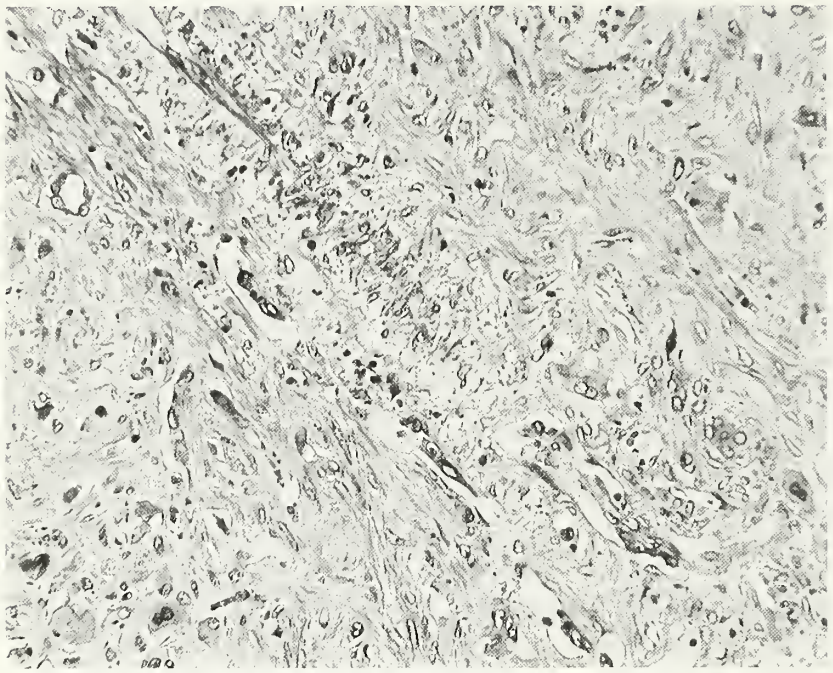


Figure 284
(Figures 284-286
are from the same patient)
EPITHELIOID
HEMANGIOENDOTHELIOMA
This malignant epithelioid hemangioendothelioma has large prominent epithelioid cells extending along the sinusoids with some spindling change and collagen deposition. The small numbers of residual hepatocytes are not very apparent except at high magnification. X245. (Courtesy of Dr. C.R. Campbell, San Mateo, California.)

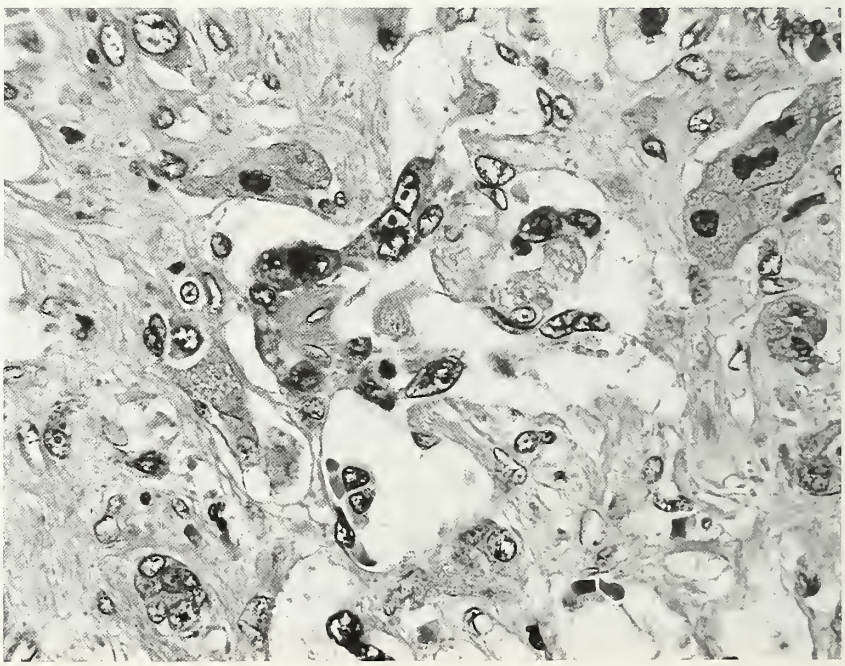


Figure 285
EPITHELIOID
HEMANGIOENDOTHELIOMA
In this figure, the hepatic malignant epithelioid hemangioendothelioma has infiltrated the sinusoids with plump endothelial cells that have abundant cytoplasm and vesicular nuclei ("epithelioid"), and there are only a few trapped hepatocytes remaining in the cords. X545. (Courtesy of Dr. C.R. Campbell, San Mateo, California.)

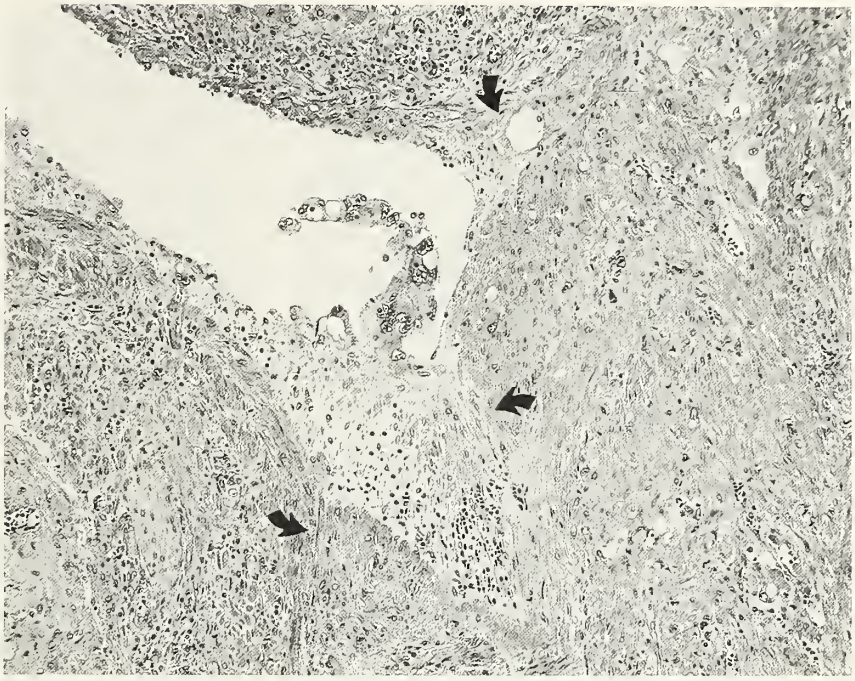


Figure 286
EPITHELIOID HEMANGIOENDOTHELIOMA
This hepatic malignant epithelioid hemangioendothelioma has partially occluded the sublobular vein (see arrows) and the surrounding bland fibrous tissue is a sclerotic area. X117. (Courtesy of Dr. C.R. Campbell, San Mateo, California.)

content, although Dean and associates reported amorphous granular material within the lumen and the lining to be blunt microvillous projections or evaginated cytoplasmic tags. The dendritic cell cytoplasm contains thin filaments and electron-dense tubular structures typical of Weibel-Palade bodies (Weiss and Enzinger).

Prognosis. Extrahepatic involvement by multicentric origin or metastasis occurs in approximately one-third of all patients, with lesions noted in the spleen, abdominal, retroperitoneal or mediastinal lymph nodes, lung, and bone. Metastatic growth appears to be more cellular than the hepatic lesions and the spindle cell component may mimic leiomyosarcoma. Extensive calcification with chondromatoid and ossifying areas may be noted in metastatic areas. Metastasis occurs more frequently in the hepatic malignant hemangioendothelioma than in the same tumor arising in the soft tissue (Ishak et al.; Weiss and Enzinger). There is no correlation of Factor VIII staining reaction and prognosis.

Survival of patients with hepatic malignant epithelioid hemangioendothelioma is considerably better than that of the conventional angiosarcoma, with 9 of 32 patients alive at 5 years regardless of treatment, whereas median survival of angiosarcoma is 5 to 6 months (Ishak et al.; Locker et al.). Long survival of 15 and 28 years has been reported with malignant epithelioid hemangioendothelioma. Hepatic transplantation has been accomplished in several patients, including patients with known metastatic tumor (Clements et al.; Marino et al.).

Differential Diagnosis. Several malignant tumors are similar including cholangiocarcinoma, metastatic signet ring carcinoma, and angiosarcoma. Epithelioid hemangiosarcoma may be primary in other locations and metastasize to the liver, making determination of the primary site a challenge. Special stains may identify carcinoma because mucin stains are negative in malignant epithelioid hemangioendothelioma, and the Factor VIII stain is diagnostic of its vascular origin. Immunoperoxidase stains for carcinoembryonic antigen and keratin are also negative in malignant epithelioid hemangioendothelioma, yet positive in carcinoma. Typical angiosarcoma is distinguished by pleomorphic, stratified spindle cells with elongated, hyperchromatic nuclei, and lacks fibrosis or epithelioid cells. In many cases of malignant epithelioid hemangioendothelioma, the fibrosis is so extensive that a needle biopsy is easily mistaken for benign fibrous tissue, and the epithelioid cells are overlooked because they are so diffuse, sparse, and intermingled within the sinusoids. One of our patients was initially classified as atypical cirrhosis (pl. X-B).

LEIOMYOSARCOMA

SYNONYMS AND RELATED TERMS: Due to a striking histologic resemblance, many published cases of fibrosarcoma may be leiomyosarcoma.

Definition. Primary hepatic leiomyosarcoma is a slowly growing, malignant tumor derived from smooth muscle cells located within the liver. The sarcomatous nature is recognized primarily by increased cellularity and variable degrees of mitotic activity. Although ultrastructural features may identify leiomyosarcoma, the characteristics are usually lacking in tumors with acceptable light microscopic features, making the distinction from fibrosarcoma difficult (Bloustein).

Incidence. Primary hepatic leiomyosarcoma is rare and usually the subject of case reports. Less than 20 patients are reported; in our series, we have five suspected leiomyosarcoma tumors.

Clinical. Of the published reports, there is an equal sex distribution and a broad age range (12 to 66 years) (Masur et al.). The typical symptoms are related to a large hepatic mass and the patients have dull right upper quadrant pain, hepatosplenomegaly, and often ascites. Liver/spleen scan reveals a filling defect. One patient had Budd-Chiari syndrome due to a large tumor arising from the hepatic vein and occluding the major hepatic outflow (MacMahon and Ball).

Pathogenesis. Intrahepatic leiomyosarcoma may be derived from the smooth muscle cells of the bile ducts or blood vessels, but traceability to such structures is destroyed by the large bulky tumor. No underlying etiologic factors are known, and the tumor is not associated with cirrhosis.

Pathology. Massive tumor at the time of diagnosis has a size range of 6 to 35 cm and the typical weight is 1 to 5 kg. The largest tumor reported was 11,270 g. The right lobe is the usual site (Fong and Ruebner). A large gray-white solitary mass with hemorrhage and necrosis is typical and a few satellite nodules may be noted. Pedunculated leiomyosarcoma has been reported and leiomyosarcoma may arise from the ligamentum teres (Mital and Bazaz-Malik; Yoshikawa et al.). The microscopic features of leiomyosarcoma are uniform spindle cells with blunt nuclear ends, red cytoplasm by Masson stain, and a variable number of

mitoses (figs. 287, 288). In some fields a few giant cells may be noted. Immunoperoxidase technics may be very helpful as the vimentin reaction is often diffusely positive. Desmin is positive in one-third of "acceptable" gastrointestinal smooth muscle tumors and a similar reactivity is expected for hepatic smooth muscle tumors (Mackay et al.). Myosin reactivity is also positive in one-third of the same group of gastrointestinal smooth muscle tumors, but these results have not been confirmed in hepatic tumors.

The electron microscopic features include the presence of dense bodies composed of definite cytoplasmic microfilaments (myofilaments) (Tomaszewski et al.). Other cytoplasmic organelles, such as mitochondria, are abundant. However, ultrastructural features are often nondiagnostic. Dense bodies are not uniformly identified in leiomyosarcoma in extrahepatic locations, and their presence is not a requirement for the diagnosis.

Differential Diagnosis. Spindle cell tumors in the liver are usually metastatic and the first consideration is to search for a primary nonhepatic leiomyosarcoma. Other primary hepatic tumors to consider are: (1) fibrosarcoma; (2) malignant fibrous histiocytoma; (3) spindle cell variant of hepatocellular carcinoma or cholangiocarcinoma; and (4) solitary fibrous mesothelioma. Sampling of the tumor is essential to characterize all the morphologic expressions as the epithelial origin of spindle cell hepatocellular carcinoma may be noted on only one slide of many (20-40) blocks. The keratin immunoperoxidase stain is negative in leiomyosarcoma and if positive (even if scattered and weakly positive), it would indicate hepatocellular carcinoma, cholangiocarcinoma or metastatic carcinoma. Fibrosarcoma is a consideration if no cytoplasmic staining is noted by the Masson stain, if there is moderate degree of cellularity, if the nuclei are tapered, and if a reticulin stain shows significant reticulin fiber between the cells. Solitary fibrous mesothelioma has less cellularity and no mitosis.

Prognosis. Surgical resection is the most effective method of treatment, but is usually not possible because of massive tumor. The majority of patients have recurrent massive hepatic tumor and some have widespread metastasis to the lungs, pancreas, peritoneal surfaces, thyroid, adrenal glands, and kidney (Fong and Ruebner).

Variants. Leiomyosarcoma arising from the ligamentum teres is a distinctive subtype since the gross configuration is a pedunculated mass which is easily resected, sometimes with adjacent structures including the left lobe of the liver. The clinical course is usually benign. Of the six reported patients, four were last reported free of disease (Tomaszewski et al.).

MALIGNANT SCHWANNOMA

SYNONYMS AND RELATED TERMS: Malignant neurilemoma; neurofibrosarcoma; neurogenic sarcoma.

Definition. Malignant schwannoma is a malignant tumor derived from Schwann cells or nerve sheath cells. Approximately 50 percent of the cases occur with von Recklinghausen's disease (diffuse neurofibromatosis) (Sordillo et al.).

Incidence. Primary hepatic malignant schwannoma is very rare, and only two published cases are known (Lederman et al.; Young). Neurofibromatosis involving the liver is relatively rare, and both reported hepatic malignant schwannomas are associated with neurofibromatosis.

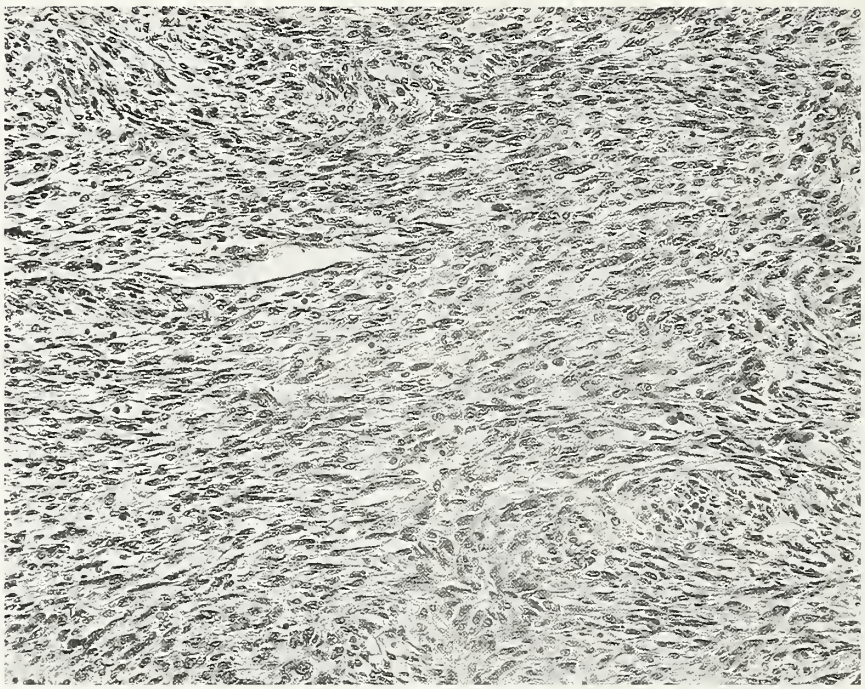


Figure 287
(Figures 287 and 288 are from the same patient)
LEIOMYOSARCOMA

This hepatic leiomyosarcoma has elongated spindle-shaped cells with cigar-shaped nuclei. The 64 year old man had a 20 cm hemorrhagic mass in the left lobe. He died 6 months later with rupture of the remaining tumor. X235. (Courtesy of Dr. Clifford Urban, Phoenixville, Pennsylvania.)

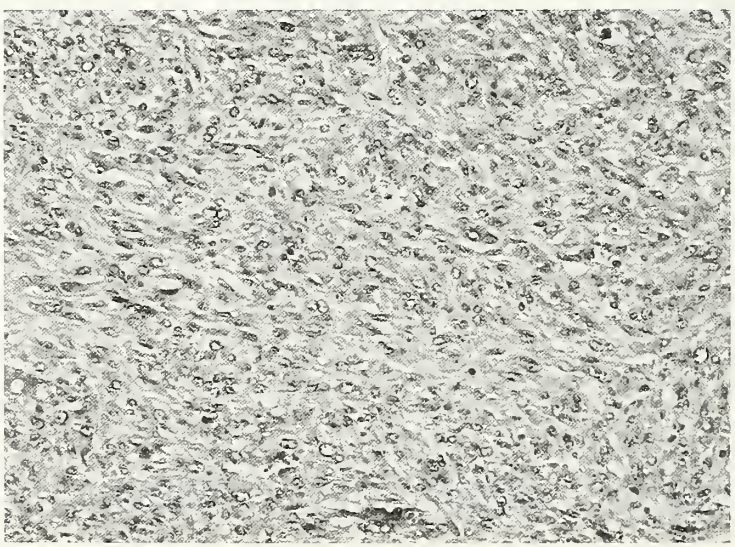


Figure 288
LEIOMYOSARCOMA

In this figure, hepatic leiomyosarcoma has interlacing bundles of spindle cells. There is a moderate degree of cellularity and the individual cells do not have distinct cytoplasmic borders. The nuclei are elongated and mitoses are not noted in this field. X620. (Courtesy of Dr. Clifford Urban, Phoenixville, Pennsylvania.)

Clinical. The two examples of hepatic malignant schwannoma occurred in men, ages 21 and 23 years, and both had café-au-lait spots and a long history of kyphoscoliosis. Jaundice and abdominal pain occurred in one patient (Young), and abdominal pain, fever, and chills simulating hepatic abscess occurred in the other (Lederman et al.). Both patients had evidence of cutaneous neurofibromata. The chest radiographs were clear of apparent metastatic disease.

Pathogenesis. The origin of the numerous peripheral neurofibromata and subsequent malignant transformation is not understood. A role for oncogenes has been suggested and the clonal origin of malignant schwannoma has been described based on glucose-6-phosphate dehydrogenase deficiency (Nevius and Friedman). The presence of angiosarcoma in malignant schwannoma is rare and occurred in one patient.

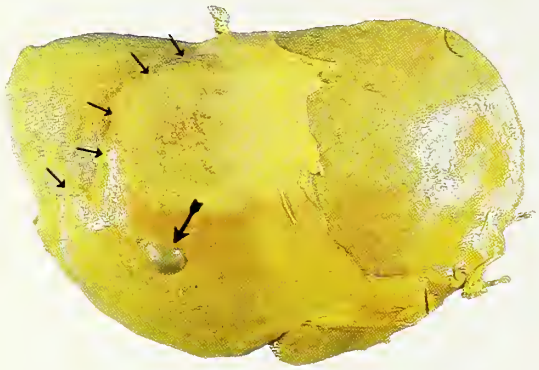
Pathology. Large hepatic tumors (20 cm in diameter and 20x30 cm) with foci of hemorrhage and necrosis were noted in both malignant schwannomas. In one patient, several small nodules of white tumor were present in the rest of the liver, and in the other case, multiple pearly-white nodules bulged into the biliary channels and into major hepatic veins (pl. X-C). An extensive area of hemorrhagic, necrotic, and gelatinous tumor extended to the peritoneal surface and was the source of bloody abdominal fluid. The tumor had a varied color and consistency, with firm, partly necrotic areas, purple and maroon areas, and tan-white gelatinous areas. Both lobes of the liver were involved. In addition, the lungs contained numerous purple and maroon metastases, which were angiosarcoma.

Microscopic features of the two tumors reveal benign neurofibromatosis with transition to malignant schwannoma. The neurofibromata are large bundles of bland nerve fibers with a variable amount of collagen (fig. 289). The cellularity of larger plump spindle nuclei increases with progression to malignant schwannoma (fig. 290). Mitoses are not prominent. In one patient, transition to angiosarcoma occurred with prominent vascularity and formation of small endothelial lined channels with moderate pleomorphic spindle lining cells (fig. 291). Staining for the S-100 protein is positive in the benign neurofibroma areas, there are scattered rare positive spindle cells in the malignant schwannoma, and there is no staining in the angiosarcoma.

Variants. The presence of angiosarcoma is distinctive and may account for the metastatic disease (Lederman et al.).

Figure 289
(Figures 289-291 and Plate X-C are from the same patient)
MALIGNANT SCHWANNOMA
These benign neurofibromas in the major portal area have a bland appearance produced by large, well-circumscribed nodules of spindle cells typical of neural proliferation. X40. (Courtesy of Dr. J. Lefkowitch, New York, New York.)

PLATE X

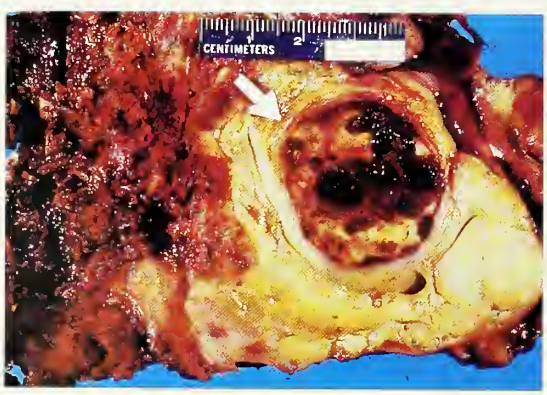


A. MAJOR DUCT CHOLANGIOCARCINOMA
(Plate X-A and figures 258 and 259 are from the same patient)

The major duct cholangiocarcinoma arising from the right hepatic bile duct produced atrophy of the right lobe and hypertrophy of the lateral and medial segments of the left lobe (arrows). An incidental solitary cyst is identified with a large arrow.

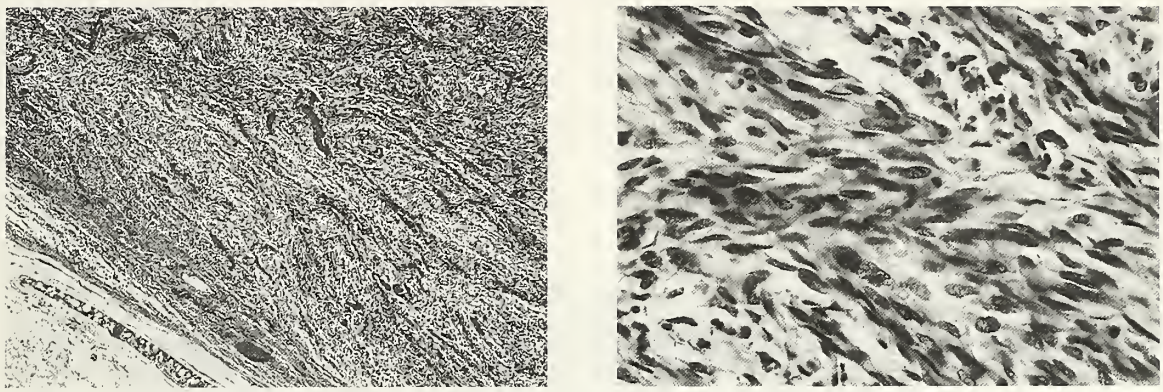
B. EPITHELIOID HEMANGIOENDOTHELIOMA

This malignant epithelioid hemangioendothelioma occurred in a 58 year old man who had an hepatic mass in 1958 and died 4 years later with hepatic failure and ascites. The gross apearance of the liver is a fibrous capsule several mm in thickness and there is replacement of the left lobe by dense white sclerosis. There is a striking resemblance to cirrhosis and the malignant features are not easily discerned.



C. MALIGNANT SCHWANNOMA
(Plate X-C and figures 289-291 are from the same patient)

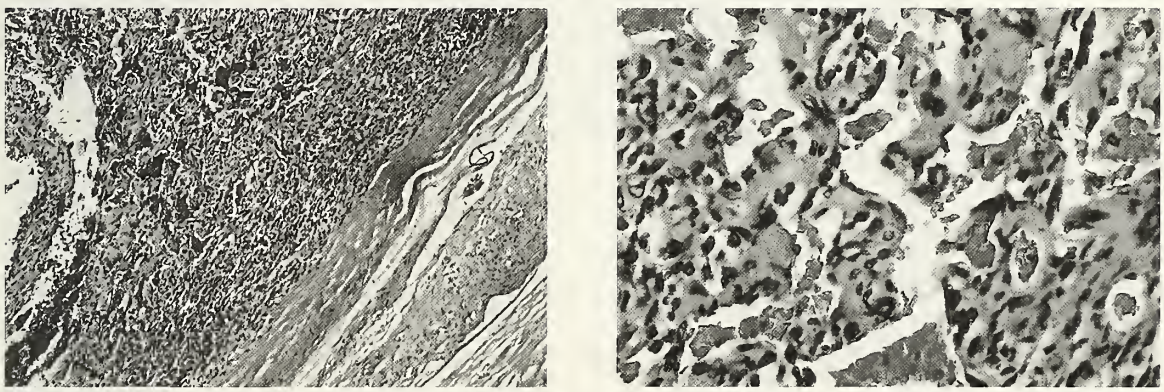
In this figure, the gross appearance of a malignant schwannoma (lower right) is white and the angiosarcoma on the left (hemorrhagic) has vascular invasion. (Courtesy of Dr. J. Lefkowitch, New York, New York.)



A B

Figure 290
MALIGNANT SCHWANNOMA

A. This area of a malignant schwannoma has a moderate degree of cellularity composed of spindle cells arranged in fascicles, and the nodule is well-circumscribed by a fibrous capsule. X85. B. This is a higher magnification of the malignant schwannoma with dense cellular spindle cells that have hyperchromatic nuclei. Mitoses are present as small irregular (not spindle-shaped) hyperchromatic nuclei that are not easily identified in a photomicrograph. X840. (Courtesy of Dr. J. Lefkowitch, New York, New York.)



A B

Figure 291
MALIGNANT SCHWANNOMA WITH ANGIOSARCOMA

A. This figure shows a malignant schwannoma area with increased cellularity and vascular spaces, highly suggestive of an angiosarcoma. A fibrous capsule surrounds the tumor. X85. B. A higher magnification of the malignant schwannoma area shows hyperchromatic nuclei in spindle cells that protrude into small vascular channels. This pattern is typical of angiosarcoma. X420. (Courtesy of Dr. J. Lefkowitch, New York, New York.)

Differential Diagnosis. The presence of spindle cell sarcoma in a patient with neurofibromatosis is usually traceable to a benign neurofibroma, and thus recognizable as malignant schwannoma. However, without the benign neurofibroma to assist in tracing the cell of origin, the spindle cell pattern resembles leiomyosarcoma, fibrosarcoma, and malignant fibrous histiocytoma. Distinction of these other sarcomas is suggested by the presence of S-100 staining (usually malignant schwannoma), lack of filamentous structures by electron microscopy (leiomyosarcoma), and lack of a storiform pattern (malignant fibrous histiocytoma).

Prognosis. The two reported patients had short clinical courses of a few months. Chemotherapy response is poor (Sordillo et al.).

FIBROSARCOMA

SYNONYMS AND RELATED TERMS: Mesothelioma (fibrosarcoma type).

A review of published photographs suggests the possible reclassification of many reported fibrosarcomas as malignant fibrous histiocytomas, leiomyosarcomas or benign fibromas. However, an accurate diagnosis is difficult due to the lack of complete sampling of the tumor, the lack of specific markers (either by immunochemical means or by electron microscopy), and the lack of information regarding mitotic count as a determinant of malignancy.

Definition. Fibrosarcoma, as defined for the soft tissue tumor, is a malignant tumor of fibroblastic origin. However, a wide variety of histologic appearances have been illustrated in the past and current criteria restrict this diagnosis to a spindle cell tumor, usually with interweaving fascicles ("herringbone") and only mild variation in nuclear size and shape. Collagen deposition may be significant and the transition of benign fibroma to a well-differentiated fibrosarcoma is difficult to recognize.

Incidence. Less than 25 cases are reported in the literature.

Clinical. Patient age ranges from 30 to 73 years and 85 percent are males (Alrenga, 1975b). A large abdominal mass is the primary clinical manifestation and a few patients have recurrent hypoglycemia (Gen et al.; Nevius and Friedman).

Pathogenesis. It is possible that this spindle cell tumor originates from the submesothelial layer of Glisson's capsule since it resembles malignant fibrous mesothelioma of the pleura.

Pathology. Hepatic fibrosarcomas are large bulky tumors with hemorrhage and necrosis producing rupture in some. Cystic degeneration may occur (fig. 292). One large tumor was 15 kg (Ishak). The microscopic features are the "herringbone" pattern (fig. 293), a mixture of broad fibrous collagenous bundles, and spindle cells without much nuclear variability (fig. 294). Mitotic activity is not prominent, although marked cellularity does occur.

Differential Diagnosis. Leiomyosarcomas are distinguished by the absence of reticulin fibers between the spindle cells, and nuclei with blunt ends (fig. 295). Malignant fibrous histiocytomas have more variation in spindle cell size with some pleomorphic small and large cells, as well as vacuolated cells. Benign fibromas are distinguished by a lack of dense cellularity and absence of local invasion.

Figure 292
FIBROSARCOMA

This well-differentiated fibrosarcoma is closely related to Glisson's capsule from which it probably arose, and the parenchyma has multiple nodules of fibrous white tissue with scattered cyst-like spaces. This large tumor weighed 3068 g and was resected from a 16 year old female. (Fig. 119 from Fascicle 25, First Series.)

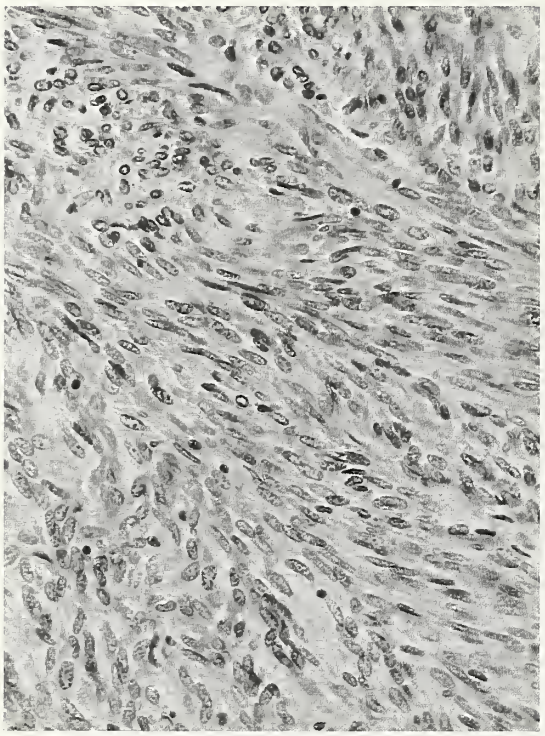


Figure 293
FIBROSARCOMA

This fibrosarcoma was associated with hypoglycemia. There is an interweaving of bundles of spindle cells that are moderately abundant and cytoplasmic borders are indistinct. Mitoses are not easily identified. X275. (Fig. 121 from Fascicle 25, First Series.)

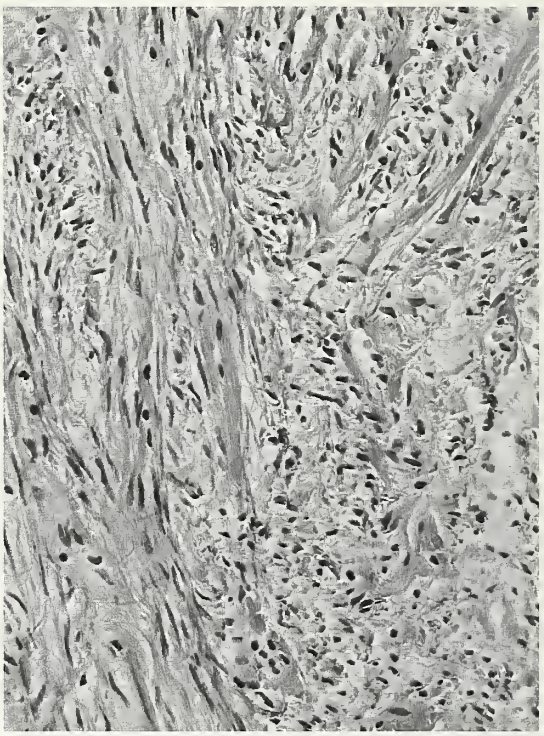


Figure 294
FIBROSARCOMA

One area of this fibrosarcoma has a moderate amount of thick, heavy collagen bands intermixed with long, slender fibroblasts. Mitoses were not seen in this area. X300. (Fig. 120 from Fascicle 25, First Series.)

Figure 295
FIBROSARCOMA

This fibrosarcoma has heavy collagen deposition around spindle cells with pointed nuclei. This 59 year old man had hypoglycemia that was relieved by tumor resection. Several years later, the hypoglycemia with the tumor recurred and was resected. He died approximately 10 years after the first resection of recurrent tumor. Masson trichrome. X545. (Courtesy of Dr. James Magidson, Patchogue, New York.)

MALIGNANT FIBROUS HISTIOCYTOMA

Malignant fibrous histiocytoma of the liver is a recently described entity; several published photographs may have used the terms fibrosarcoma, leiomyosarcoma, and undifferentiated sarcoma instead of malignant fibrous histiocytoma (Alberti-Flor et al.). Malignant fibrous histiocytoma of the liver is similar in histologic appearance to malignant fibrous histiocytoma in soft tissue and is composed of spindle cells arranged in a storiform pattern. Moderate degree of pleomorphic spindle cells and giant cells are common, as well as vacuolated cells. In one reported hepatic malignant fibrous histiocytoma, the predominant histologic pattern was moderately large spindle cells with marked variation in nuclear size and shape (figs. 296, 297). Two reported tumors are large (2100 and 2900 g) and appear as either a solitary mass or multiple nodules (Conran and Stocker).

Metastatic malignant fibrous histiocytoma from soft tissue (retroperitoneum or extremity) is a major consideration. Undifferentiated sarcoma has some similar features, but lacks both the storiform pattern of spindle cells and the giant cell component.

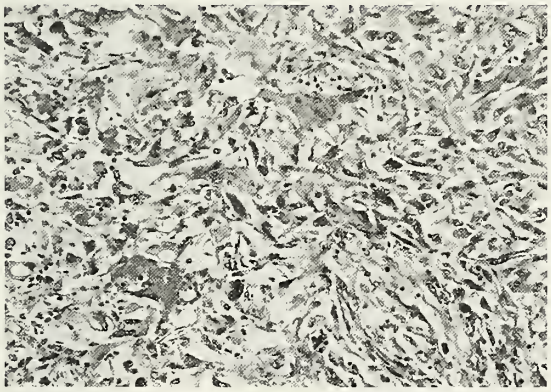


Figure 296
(Figures 296 and 297 are from the same patient)
MALIGNANT FIBROUS HISTIOCYTOMA
This malignant fibrous histiocytoma of the liver has moderate variation in spindle cell size and shape with nuclear pleomorphism. The spindle cells grow in fascicles of interlacing bundles. Other fields had marked necrosis. X420. (Courtesy of Drs. J.J. Alberti-Flor and Susan Halter, Nashville, Tennessee.)

Figure 297
MALIGNANT FIBROUS HISTIOCYTOMA
This malignant fibrous histiocytoma extends into the adjacent liver cords, and the spindle cells have marked variation in nuclear shape. Other fields have spindle cells with foamy vacuolated cytoplasm. X1240. (Courtesy of Drs. J.J. Alberti-Flor and Susan Halter, Nashville, Tennessee.)

LYMPHOMA

SYNONYMS AND RELATED TERMS: Malignant lymphoma; lymphosarcoma.

Definition. Primary hepatic lymphoma is a malignant tumor with lymphoid markers (T or B cell origin), and is limited to the liver without evidence of lymph node or extrahepatic spread. The lymphoma may have moderately large, polygonal cells with scant or abundant cytoplasm and irregular nuclei.

Incidence. A few reports were published, but it wasn't until 1985 that several larger series appeared and by 1987, more than 28 patients were described (DeMent et al.; Gaulard et al.; Osborne et al.). The Johns Hopkins Tumor Registry file indicates six cases in a 30 year period, which is 1.1 percent of all primary hepatic tumors in the series.

Clinical. Patients range in age from 8 to 84 years and the average age is 50 to 60 years. Males predominate, accounting for 19 of the 28 patients (DeMent et al.). Major symptoms include fever, weight loss, abdominal pain, and abdominal mass. The clinical evaluation reveals a solitary large tumor, multiple tumor nodules or occasionally, diffuse enlargement of the liver. Biopsy and diagnosis of the tumor leads to more extensive staging that must demonstrate hepatic involvement as the dominant tumor burden, without spread to other organs or lymph nodes. Diffuse hepatic involvement occurs with peripheral T cell lymphoma and may occur without the usual skin, lymph node, and peripheral blood involvement (Gaulard et al.).

Pathogenesis. The evolution of lymphoma from hepatic lymphocytes is not well understood and may be the result of lymphocytic neoplasia occurring outside the liver with predominant growth within the liver. Whereas the histologic patterns vary and include both T and B cell derivation as well as diffuse and nodular variants, the large cell lymphocytic type is more common in primary hepatic lymphoma. The presence of a chronic inflammatory disease such as cirrhosis is not related since only a few primary hepatic lymphomas occur with cirrhosis. Primary hepatic lymphomas may occur with AIDS.

Pathology. The gross appearance of primary hepatic lymphoma varies from a large solitary mass with necrosis or central fibrosis, to multiple white nodules, and to diffuse hepatomegaly without distinct mass lesions. Solitary large lesions may be as large as 20 cm in diameter and often are resected.

A broad range of microscopic patterns typifies lymphoma in other organs, but diffuse large cell lymphoma involving portal areas and large masses are the most common form of primary hepatic lymphoma (figs. 298, 299). Large cells with large nuclei and large nucleoli are mixed with small lymphocytes and proliferate around bile ducts and other portal structures. The adjacent hepatocytes are usually sharply demarcated, and the sinusoids may have only limited Kupffer cell hyperplasia or may also be lined by abnormal lymphoid cells that require immunotyping to demonstrate their monoclonal origin. Peripheral T cell lymphoma extends into the sinusoids as chains of cells as well as large masses in the lobule (Gaulard et al.). A needle biopsy may demonstrate only sheets of abnormal monomorphous cells that mark as monoclonal lymphoid antigens (fig. 300). Large lesions are often difficult to obtain good formalin fixation, and thus cytologic detail may be poor, resulting in

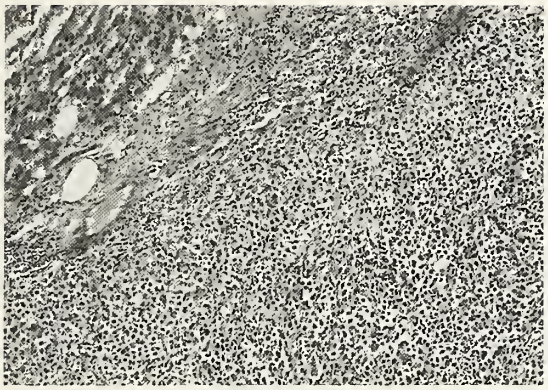


Figure 298
(Figures 298 and 299 are from the same patient)
PRIMARY HEPATIC LYMPHOMA

Immunochemistry confirmed the lymphoid derivation of this large cell pleomorphic tumor with positive reaction for Leukocyte Common Antigen, B and kappa antigen, as well as negative reactions for cytokeratins and T cell antigen. X85. (Courtesy of Dr. Fred Villamil, Buenos Aires, Argentina. Immunochemistry by Dr. Gregorio Chejfec, Chicago, Illinois.)

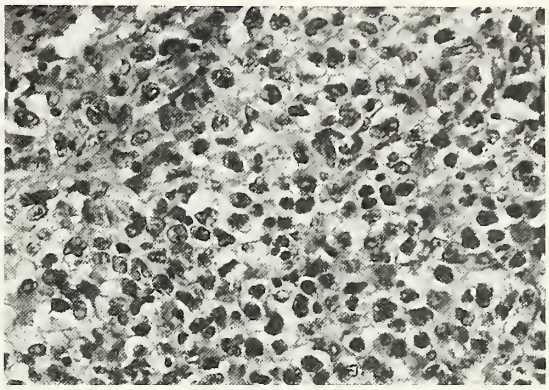


Figure 299
PRIMARY HEPATIC LYMPHOMA

A higher magnification of the primary hepatic lymphoma in figure 298 shows intermediate size lymphocytes with irregular nuclei and no nuclear grooves. The cytoplasm is moderately abundant. X840. (Courtesy of Dr. Fred Villamil, Buenos Aires, Argentina.)

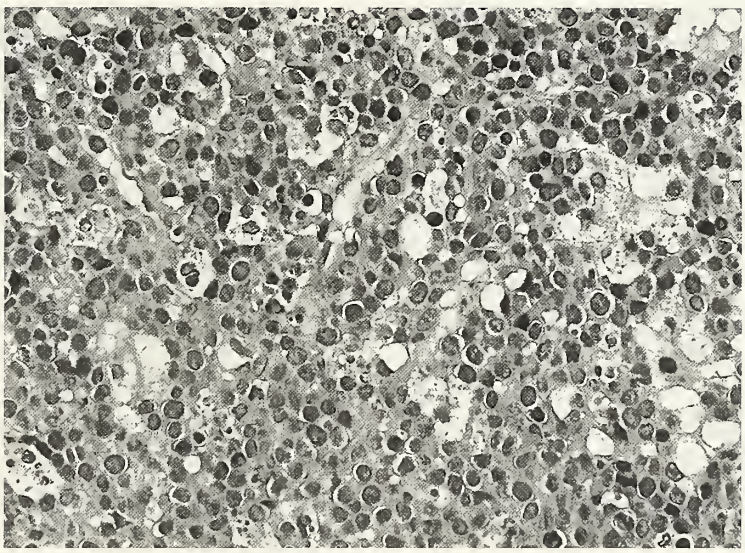


Figure 300
PRIMARY HEPATIC LYMPHOMA

A needle biopsy of a primary hepatic lymphoma reveals only broad sheets of blastoid cells with mitoses and a starry-sky pattern typical of Burkitt's-like lymphoma. This is case 1 from Verdi with immunophenotyping of pre-B cell origin. X1240. (Courtesy of Dr. Thomas Grogan, Tucson, Arizona.)

difficulty in classification. Immunochemical studies to demonstrate lymphoid markers, including common leukocyte antigen, T and B cell antigens, kappa and lambda markers, and other antigens, are required to prove the lymphoid origin of these often pleomorphic tumors (figs. 298, 300).

Differential Diagnosis. Pseudolymphoma, which is an extensive benign lymphoid hyperplasia occurring as a solitary mass, may mimic primary hepatic lymphoma. Application of immunologic markers may demonstrate polyclonal lymphocytes in pseudolymphoma, and immunotyping is very helpful in the diagnosis of primary hepatic lymphoma (Verdi et al.). The presence of lymphoid follicles (histiocytes and immunoblasts admixed with small and large lymphocytes) within a portal area is most likely a benign reactive feature. Hepatocellular carcinoma obtained in either small amounts or distorted by fixation may be mistaken for primary hepatic lymphoma (DeMent et al.).

Course. Several of the large primary hepatic lymphoma masses have been resected and additional chemotherapy and/or radiation therapy has been given, usually with favorable results. A rapid and fatal course with widespread disease has been reported in a few patients. However, some patients have no other extrahepatic disease noted for many months and appear free of disease for several years. In patients with diffuse involvement or multiple masses of lymphoma, resection is impractical, and chemotherapy may be the best treatment.

OSTEOSARCOMA

Definition. Primary hepatic osteosarcoma is a primary hepatic tumor composed predominantly of bone-forming spindle cell sarcoma and only a limited amount of nonbone-forming sarcoma. Numerous sections are needed to verify that the tumor is not a variant of hepatocellular carcinoma or another type of sarcoma, such as malignant fibrous histiocytoma. Furthermore, metastatic osteosarcoma must be excluded.

Incidence. Two primary hepatic osteosarcomas have been reported (Sumiyoshi and Niho; von Hochstetter et al.) and a third case is in our files.

Clinical. The three known patients, two males and one female, are 71, 73, and 52 years old. Major symptoms were abdominal mass and intestinal obstruction, mild abdominal pain, and hepatic failure (in a patient with cirrhosis). CT scans of our patient revealed microcalcification, and a celiac angiogram showed neovascularity in the right mass and none in the left lobe.

Pathogenesis. The origin of primary hepatic osteosarcoma is unknown and numerous sections revealed no traceability to underlying benign mesenchymal tissue or to congenital anomalies. Origin from residual mesenchymal tissue has been suggested, but nontumorous mesenchymal remnants are not identified.

Pathology. Primary hepatic osteosarcomas are large tumors at the time of diagnosis; two patients had a tumor weight of 3400 and 2100 g. The parenchyma of one tumor included a large cystic cavity, approximately 20 percent of the total volume of the tumor (pl. XI-A). Because of the cuboidal epithelial lining and presence of several smaller similar cysts at the margin of the tumor, this cavity appeared to be a dilated major bile duct. More than 24 sections showed extensive osteoid formation (fig. 301) surrounded by sarcomatous stroma with giant cell formation (fig. 302)

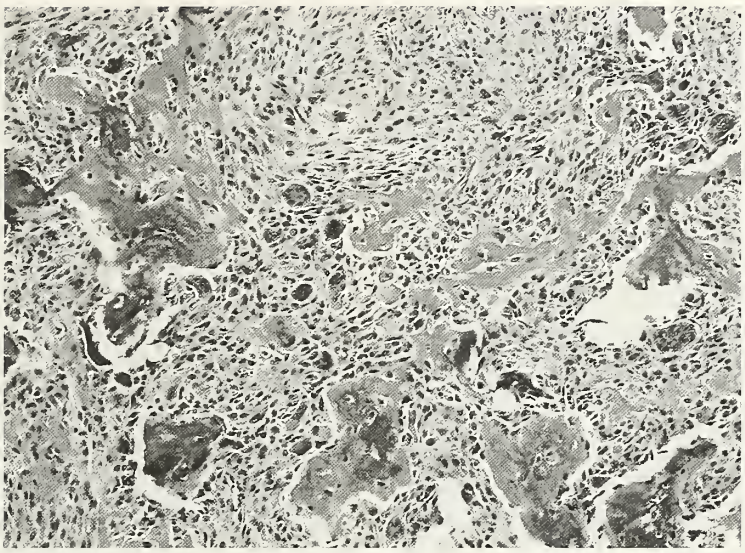


Figure 301
(Figures 301-303 and Plate XI-A are from the same patient)
PRIMARY HEPATIC OSTEOSARCOMA
This primary hepatic osteosarcoma, with osteoid surrounded by malignant stroma composed of spindle cells, shows marked nuclear pleomorphism and multinucleated giant cells. X310. (Courtesy of Drs. Steve Romansky and C. Petrie, Fullerton, California.)

and areas of fibrosarcoma. Chondrosarcoma with transition to the abundant osteosarcomatous areas was also noted. Bland fibrous tissue surrounding remnants of portal areas were noted and the large cyst had simple columnar epithelium typical of bile duct origin. At the margins of the large tumor, islands of trapped hepatic cords and portal areas were common. The adjacent liver was normal with evidence of chronic liver disease. Because the predominant histologic pattern was pleomorphic stroma with osteoid production and multinucleated giant cells, the tumor was classified as hepatic osteosarcoma (fig. 303). A specimen radiograph indicated 35 to 40 percent of the mass was calcified. No transition to hepatocellular carcinoma was detected.

Differential Diagnosis. Metastatic osteosarcoma must be excluded by search for an extrahepatic primary tumor. Numerous sections are needed to exclude metaplastic transformation of a hepatocellular carcinoma. Origin in a noncirrhotic liver indicates that the confusion with hepatocellular carcinoma is less likely. Some malignant fibrous histiocytomas have foci of osteosarcoma, but not as a predominant feature, and the presence of chondrosarcoma is very unusual for malignant fibrous histiocytoma.

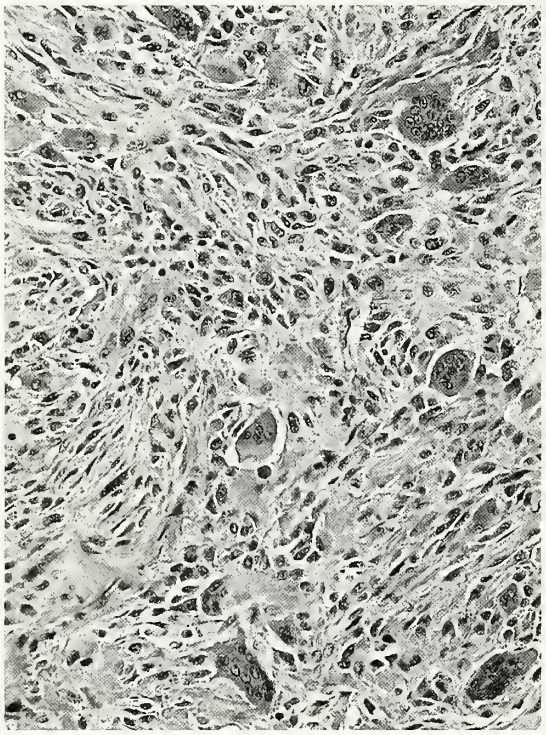


Figure 302
PRIMARY HEPATIC OSTEOSARCOMA
The multinucleated giant cells and pleomorphic stroma of primary hepatic osteosarcoma may mimic malignant fibrous histiocytoma, but the abundance of osteoid production and the large multinucleated giant cells are typical of osteosarcoma. X620. (Courtesy of Drs. Steve Romansky and C. Petrie, Fullerton, California.)

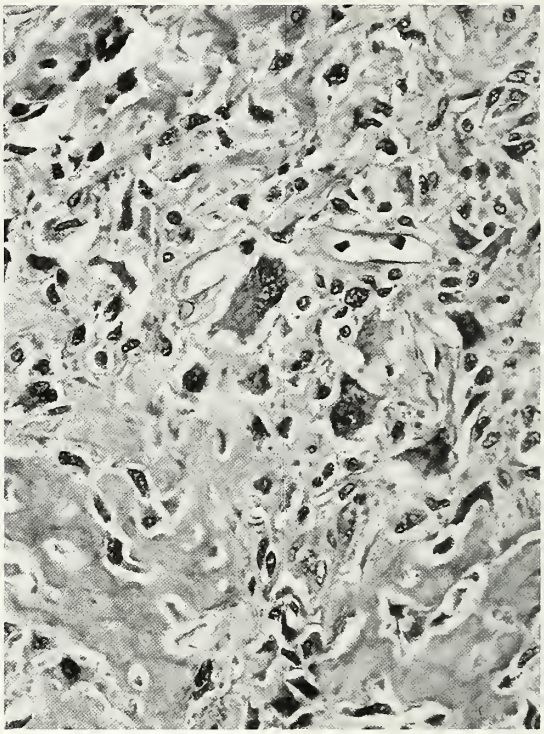


Figure 303
PRIMARY HEPATIC OSTEOSARCOMA
Intermingling of pleomorphic stroma, giant cells, and osteoid of this osteosarcoma shows the transition of the different sarcomatous patterns. X1240. (Courtesy of Drs. Steve Romansky and C. Petrie, Fullerton, California.)

RHABDOMYOSARCOMA

SYNONYMS AND RELATED TERMS: Botryoid rhabdomyosarcoma.

Definition. Rhabdomyosarcoma is a malignant tumor with primitive cells that have skeletal muscle features, such as cross striations, and proteins typical of skeletal muscle derivation, such as actin, myosin, and myoglobin. The majority of rhabdomyosarcomas in the hepatobiliary area are derived from the biliary structures and are polypoid intraductal masses. Approximately 25 percent of the tumors appear to arise within the liver rather than invade the liver from an adjacent major bile duct structure.

Incidence. Rhabdomyosarcoma of the liver is a rare sarcoma usually restricted to children; it accounted for three of eight primitive childhood hepatic sarcomas in one series (Horowitz et al.). In a review of 23 embryonal rhabdomyosarcomas of the liver and biliary system, three were considered primary within the liver (Davis et al.).

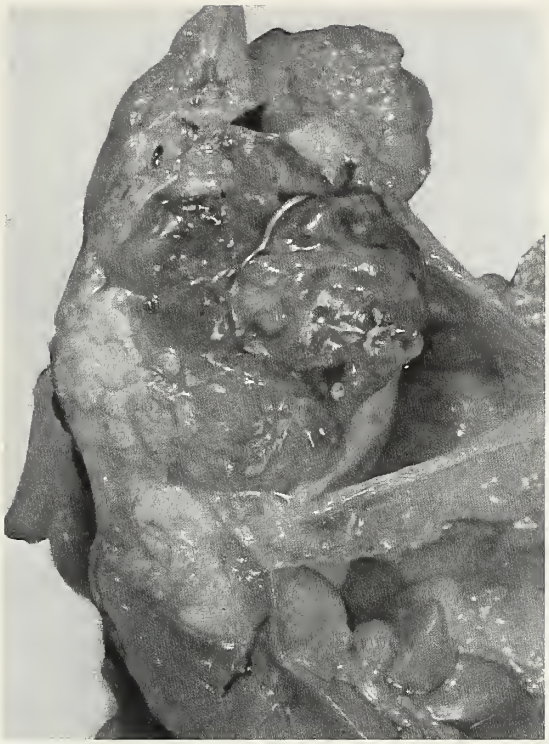


Figure 304
(Figures 304 and 305 are from the same patient)
RHABDOMYOSARCOMA
This rhabdomyosarcoma of the left lobe of the liver occurred in a 6½ week old girl. The tumor was 11x10x6 cm. (Fig. 137 from Fascicle 25, First Series.)

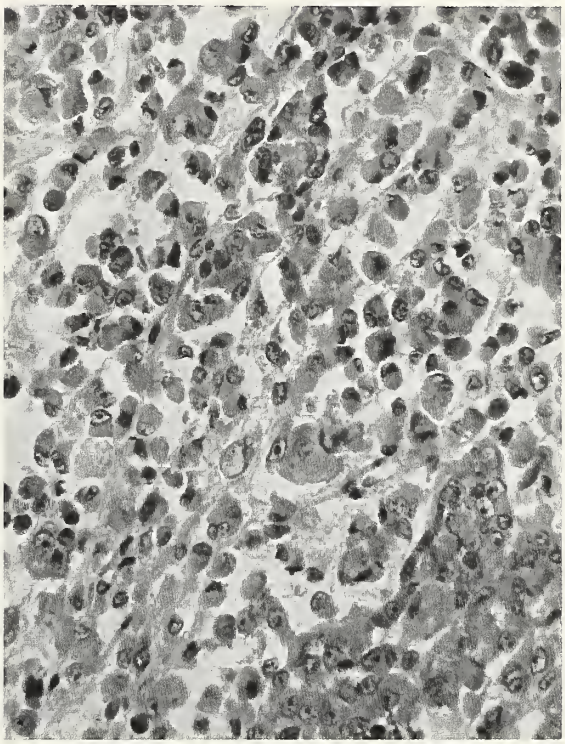


Figure 305
RHABDOMYOSARCOMA
Oval rhabdomyoblasts with abundant pink cytoplasm are the predominant cells in this field. The cells have little cohesiveness and the nuclei are round, irregular, eccentrically located, and hyperchromatic. Multinucleated and giant cells are occasionally noted. Cross striations are not easily identified. X285. (Fig. 138 from Fasicle 25, First Series.)

Clinical. Most children with biliary rhabdomyosarcoma have jaundice from the bulky intrabiliary polypoid tumor and are diagnosed prior to development of a large hepatic mass due to tumor invasion from the bile duct. However, a few patients have a large hepatic mass as the primary presenting sign and the pathologic classification may be difficult due to histologic similarity to undifferentiated (embryonal) sarcoma. Two adults have been reported with rhabdomyosarcoma (Mori et al.; Morimoto et al.).

Pathology. Rhabdomyosarcoma of the liver may be an extension of a botryoid rhabdomyosarcoma with major bile duct polypoid tumor. The tumor is pale and fleshy with cystic spaces (fig. 304). Microscopic features are rhabdomyoblasts with plump eosinophilic cytoplasm, an eccentric hyperchromatic nucleus, and an occasional cell with cross striations (fig. 305). Immunohistochemical studies help identify muscle derivation since the presence of actin, myosin, and myoglobin indicates rhabdomyosarcoma. In contrast,

actin, myosin, and myoglobin are absent in embryonal sarcoma, which is also a primitive myxoid tumor occurring in a similar age group (DeJong et al.).

Differential Diagnosis. Undifferentiated sarcoma is similar to rhabdomyosarcoma with myxoid stroma and spindle cells. The majority of these cells are small, although some may be large. By definition, no rhabdomyoblasts are present in undifferentiated sarcomas. In some pleomorphic soft tissue sarcomas, the positive immunostaining for actin, myosin, and myoglobin may allow recognition of rhabdomyosarcoma in tumors that otherwise would be considered leiomyosarcomas or malignant fibrous histiocytomas (DeJong et al.).

Prognosis. Survival is highly variable, and surgical resection provides the best hope for cure. Distant metastases are not common and progressive local spread of the tumor is the usual course. Chemotherapy has provided objective response and resection of isolated metastasis has been performed (Horowitz et al.).

MESENCHYMAL SARCOMA

SYNONYMS AND RELATED TERMS: Undifferentiated sarcoma; embryonal sarcoma; malignant mesenchymoma; fibromyxosarcoma.

Definition. Mesenchymal sarcoma is a malignant tumor occurring primarily in children. It is composed of primitive spindle cells with myxoid stroma and has no recognizable sarcomatous differentiation (no rhabdomyosarcoma or leiomyosarcoma, etc.).

Incidence. In most large series, mesenchymal sarcoma is the third or fourth most common malignant hepatic tumor in children and accounts for approximately 5 percent of primary malignant hepatic tumors (Dehner; Stanley et al.). Mesenchymal sarcoma was diagnosed in 1 percent of our overall autopsy series (see Table 1). There are 31 patients in the largest series (Stocker and Ishak).

Clinical. The typical age at diagnosis is 6 to 10 years, with 88 percent detected below 15 years of age. There is an equal sex incidence and the major clinical findings are abdominal mass, fever, and pain. Symptoms were present a few days to a month prior to discovery, and one tumor ruptured. A few asymptomatic patients had documented abdominal enlargement for a few weeks to 6 months (Stocker and Ishak). Radiographic studies reveal an avascular hepatic mass. The α-fetoprotein has been negative.

Pathogenesis. Relationship to benign mesenchymal hamartoma has been suggested; however, no traceability of mesenchymal sarcoma to the benign mesenchymal tumor has been recorded. In a few patients with incomplete resection of mesenchymal hamartoma, no progression to a pleomorphic malignant tumor has been noted (Stocker and Ishak). Because mesenchymal sarcoma has also been documented in older patients (70 years), embryonal or congenital derivation is unlikely.

Pathology. Mesenchymal sarcoma is a large tumor with hemorrhage, necrosis, cystic areas up to 4 cm in diameter, and gelatinous brown contents (fig. 306). The size at surgery varies from 7 to more than 20 cm, and the average weight in 16 tumors was 1310 g (Stocker and Ishak). Although the right lobe is usually involved, a pedunculated form has been reported. The microscopic appearance is fairly uniform in the different tumors, with a thick fibrous pseudocapsule separating the myxoid stroma that contains bile ducts and

Figure 306
UNDIFFERENTIATED SARCOMA

This undifferentiated sarcoma of the liver was removed from a 6 year old male. The myxoid tumor has fibrous bands dividing the cystic, myxoid, gray, translucent tissue into compartments. Necrosis and hemorrhage are common, but are not a major component of this cut surface. (Fig. 133 from Fascicle 25, First Series.)

occasional nests of hepatocytes from the benign normal liver. Some densely cellular areas have many small round cells with hyperchromatic nuclei without nucleoli (fig. 307). The number of anaplastic malignant cells appears greater adjacent to the duct epithelium (fig. 308). Mitoses are abundant and there are areas of myxoid stroma and necrosis. PAS stain reveals small PAS positive diastase resistant droplets (fig. 309). Spindle cells and giant cells may suggest fibrosarcoma or malignant fibrous histiocytoma, but there is variation in mesenchymal sarcoma, and other areas are myxoid stroma, trapped bile ducts with irregular dilation, and cells with PAS positive droplets.

Electron microscopy reveals primitive fibroblasts, small mesenchymal cells, small mitochondria, distended rough endoplasmic reticulum, and membrane-bound bodies which may be α-1-antitrypsin or antichymotrypsin (Abramowsky et al.). Immunoperoxidase reveals the stroma is negative of desmin, but positive for vimentin (Keating and Taylor).

Figure 307
(Figures 307 and 309 are from the same patient)
UNDIFFERENTIATED SARCOMA
Undifferentiated sarcoma has a very cellular area near the fibrous capsule. Small bile ducts are "trapped" by the expanding tumor, the many small cells do not have cytoplasmic borders, and the hyperchromatic nuclei lack nucleoli. X620.

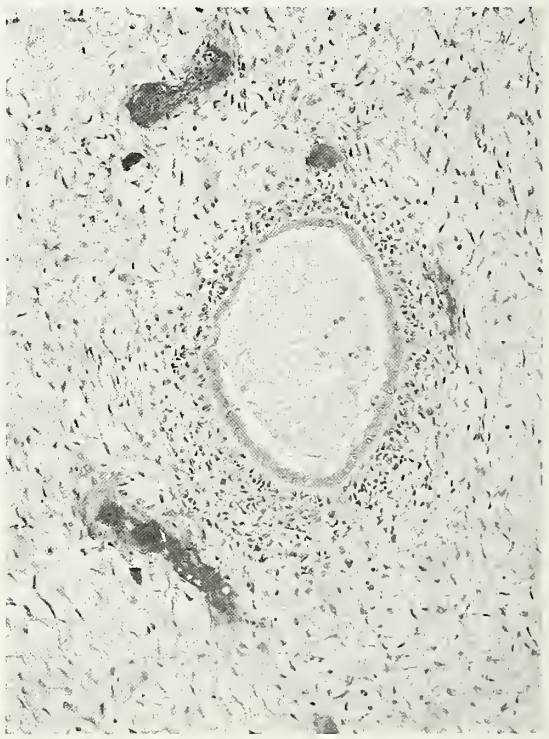


Figure 308
UNDIFFERENTIATED SARCOMA
This undifferentiated sarcoma has myxoid areas with dilated ducts surrounded by slightly more cellular stroma. Although this appearance is suggestive of embryonal rhabdomyosarcoma, no cross striations within any of numerous slides were detected. X620.

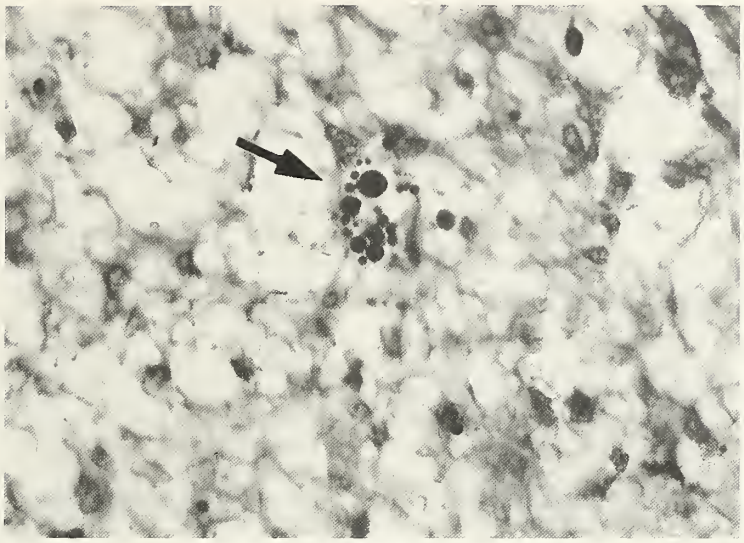


Figure 309
UNDIFFERENTIATED SARCOMA
This undifferentiated sarcoma has PAS positive diastase resistant droplets within the cytoplasm. PAS. X1240.

Differential Diagnosis. Several tumors are confused with mesenchymal sarcoma including malignant fibrous histiocytoma and mesenchymal hamartoma, and a limited sample may mimic a fibrosarcoma or leiomyosarcoma. No storiform pattern is noted in mesenchymal sarcoma, as is typical for malignant fibrous histiocytoma. The pleomorphic stellate cells are not seen in the benign, bland-appearing mesenchymal hamartoma. The presence of the cysts (dilated bile ducts) and the myxoid stroma are not noted in either leiomyosarcoma or fibrosarcoma of the liver.

Prognosis. Resection is the best hope for cure, although even if the surgical resection margins are clear, recurrence is observed (Dehner). Distant metastasis to the lung is common and the average survival is 11 months (Stocker and Ishak). Pulmonary metastases are myxoid stroma without any glandular elements. Although the tumors are large at discovery, chemotherapy has been useful in reducing the tumor size, thus allowing a hepatic resection (Harris et al.). Based on published reports, 70 percent of patients have died of the tumor, and only 17 percent are alive without evidence of disease.

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METASTATIC TUMORS

Metastatic tumors to the liver have origins from both epithelial and mesenchymal tissues of the body, but epithelial tumors are far more common and proliferate readily within the liver. Distinction of primary tumor from metastatic tumor may be difficult in selected tumors and may not be resolved by exacting histologic technics. Even after autopsy, the exact origin of some tumors may not be determined.

Definition. Metastatic hepatic tumor is derived from extrahepatic tissue and spreads to the liver by vascular channels (portal or hepatic vessels and lymphatic vessels) or by peritoneal fluid with subsequent proliferation. The primary origin may be occult.

Incidence. In the United States, metastatic carcinoma occurs far more commonly than primary hepatic carcinoma. In the large series of 94,556 autopsies at the LACUSC-MC and USC Liver Unit from 1918-1980, malignant extrahepatic tumors occurred in 20.4 percent (19,208) of the patients, and 38 percent (7299) of those had hepatic metastasis. A large cancer referral center reported 9700 cancer autopsies, 75 percent with metastasis and 41.4 percent with hepatic metastasis (Pickren et al.). In contrast, there were 405 primary hepatic malignant tumors (0.4 percent) in the USC series. Thus, metastatic tumor to the liver was 18 times more common than primary malignant tumor. In the large Roswell Park Memorial Institute series, metastatic tumor to the liver was 41 times more common than primary hepatic tumor (Pickren et al.). Metastatic sarcoma to the liver is far more common than primary hepatic sarcoma. In the Roswell Park series, 113 of 333 (34 percent) sarcomas had hepatic metastasis at autopsy (Pickren et al.).

Clinical. The clinical manifestations of metastatic carcinoma to the liver are highly variable and are of special interest if symptoms of primary hepatic disease occur because the specific tumor location and type often are obscure. Jaundice is not an early sign in most patients except for those with carcinoma derived from the gallbladder, common bile duct, head of pancreas, and stomach. Jaundice may be due to tumor growth in a specific location that occludes the common bile duct, yet it is common in terminal cancer patients with extensive metastasis and almost total replacement of the liver by the tumor. Table 13 lists the metastatic tumors to the liver and the incidence of icterus at autopsy in the LACUSC-MC and USC Liver Unit autopsy series. The relative incidence of icterus at autopsy in metastatic tumor is tabulated in Table 14. Approximately one-third of the patients have no recognizable cause of jaundice because: (1) there is no bile duct involvement; (2) less than 60 percent of the liver is replaced by the tumor; and (3) there is no evidence of pigment overload (e.g., no hemolysis). Furthermore, about 50 percent of the patients with hepatic metastasis at autopsy have no signs or symptoms of liver disease. On the other hand, the liver was the sole site of metastasis in only 0.8 percent. A single hepatic metastasis occurred in only 6 percent of the series of Pickren and associates.

The most common tumors in our series to metastasize to the liver are listed in Table 13. Bronchogenic carcinoma is the most common origin for metastatic

Table 13

MOST COMMON NONLYMPHOMA METASTATIC MALIGNANT TUMORS IN LIVER AND DEVELOPMENT OF JAUNDICE*

Tumor	Number of Primary Tumors	Number of Tumors with Hepatic Metastases	Percent of Tumors with Hepatic Metastases	Percent of Patients with Hepatic Metastases Who Were Icteric
Bronchogenic	682	285	41.8	9
Colon	323	181	56.0	34
Pancreas	179	126	70.4	51
Breast	218	116	53.2	30
Stomach	159	70	44.0	60
Unknown primary	102	59	57.0	35
Ovary	97	47	48.0	0
Prostate	333	42	12.6	0
Gallbladder	49	38	77.6	60
Cervix	107	34	31.7	10
Kidney	142	34	23.9	15
Melanoma	50	25	50.0	13
Urinary bladder and ureter	66	25	37.9	11
Esophagus	66	20	30.3	29
Testis	45	20	44.4	14
Endometrial	54	17	31.5	< 20
Thyroid	70	12	17.1	14

* Modification of table 33-1 from Edmondson, H.A. and Craig, J.R. Neoplasms of the Liver. In: Diseases of the Liver, 6th ed. Schiff, L. and Schiff, E.R. (Eds.). New York: J.B. Lippincott Company, 1987.

carcinoma, although icterus is more common with colon origin due to a greater hepatic tumor burden at the time of death. Occult primary tumors that produce hepatic symptoms often have origins in the pancreas, lung, and stomach, but with greater use of specialized procedures, they are less common at autopsy. Although many tumors such as those primary in the breast and colon are detected first for local disease rather than for liver signs, the recurrence of tumor after initial treatment is often noted by hepatic signs.

Pathogenesis. Metastases reach the liver by vascular spread (portal vein, hepatic artery) and rarely by abdominal fluid (ascites). Organs with portal venous drainage have a much greater incidence of hepatic metastasis than organs without portal venous drainage (Pickren et al.). Of the organs that lack portal venous drainage and have a high metastatic potential to the liver, the breast, eye (melanoma), lymph node, testis, and bone marrow tumors are important (Pickren et al.). The liver is second only to the lymph nodes as a site for proliferation of metastatic tumor. Thus, the liver is suitable for proliferation and attachment of circulating tumor cells which, by virtue of the vascular system, are distributed to numerous organs. The presence of cirrhosis seems to reduce the incidence of metastatic tumor to the liver

Table 14

RELATIVE FREQUENCY AND CAUSE OF ICTERUS IN METASTATIC CARCINOMA TO LIVER*

Site of Primary Tumor Per 100 Icteric Tumor Patients	Number of Tumors	Percent of Patients		
		Cause of Icterus by > 75 Percent of Hepatic Replacement	Cause of Icterus by Duct Involvement by Tumor	Cause of Icterus by < 60 Percent of Hepatic Replacement, Unknown
Colon	21	86	6	9
Pancreas	21	11	45	43
Stomach	14	33	11	56
Breast	12	72	17	11
Unknown primary	9	83	< 1	17
Bronchogenic	8	30	20	50
Gallbladder	3	21	43	36
Hodgkin's	3	0	3	97
Bile duct	3	< 1	100	< 1
Melanoma	1	67	33	< 1

* Modification of table 33-2 from Edmondson, H.A. and Craig, J.R. Neoplasms of the Liver. In: Diseases of the Liver, 6th ed. Schiff, L. and Schiff, E.R. (Eds.). New York: J.B. Lippincott Company, 1987.

(Gall) and the type of cirrhosis influences the incidence. For example, biliary cirrhosis has a higher incidence of metastatic tumor than other types of cirrhosis. The metastatic intravascular or sinusoidal tumor cells proliferate in the liver, are adherent to the sinusoid wall, and new vessels develop. The portal venous supply is less important as the metastatic tumor grows and stimulates new arterial supply, but with ligation of the hepatic artery, the dependence on portal venous blood allows continued growth. Almost 60 percent of the metastatic tumor nodules in the liver have a portal venous supply at the periphery of the nodules (Strohmeyer et al.).

Pathology. The gross features of a metastatic carcinoma are often typical for a group of primary tumors (Table 15) (pl. XI-B, figs. 310-313). Some gross features are helpful in distinguishing metastatic tumor from hepatocellular carcinoma and cholangiocarcinoma. Umbilication, not limited to large metastases, is a central depression noted on the hepatic surface that is produced by necrosis or fibrous scarring of the central area (fig. 310). The rim is slightly or moderately raised with a serrated border and is often a different color than the depressed portion. The cut surface shows the central area in varying stages of necrosis, which may be liquefactive necrosis if large (fig. 311) or fibrosis with a redder periphery due to hyperemia (pl. XI-B). Umbilication is common in metastatic adenocarcinoma and is not noted in pure hepatocellular carcinoma. The margins of such umbilicated nodules stand out well if the border is more vascularized than the pale granular center. Cholangiocarcinoma tends to lack the hyperemic rim.

Table 15

MORPHOLOGIC PATTERNS OF METASTATIC TUMORS TO LIVER*

Morphologic Pattern	Site of Primary Tumor	Hepatic Signs or Symptoms
1. Expanding		
A. Massive (solitary, with satellites or multiple foci)	colon gallbladder testis	+ or -
B. Uniform nodular	lung melanoma pancreas	-
2. Infiltrative		
A. Massive	lung breast pancreas urinary bladder melanoma	+ or -
B. Uniform multifocal	breast pancreas lung melanoma	-
C. Diffuse	breast pancreas lymphoma	+ or -
3. Surface spreading	colon ovary occasionally, stomach	-
4. Incidental	any	-
5. Miliary	prostate occasionally, any	-
6. Mixed or indeterminate	any	+ or -

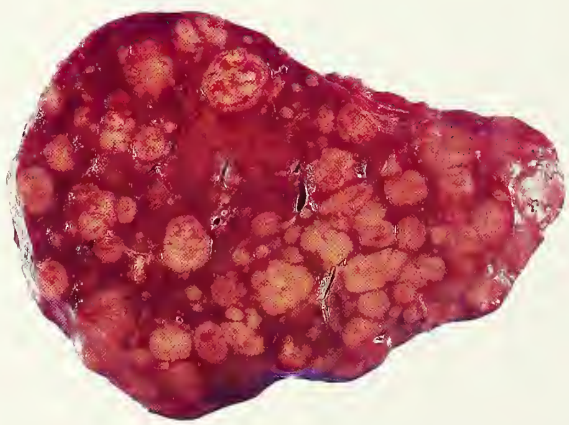
* Modification of table 33-3 from Edmondson, H.A. and Craig, J.R. Neoplasms of the Liver. In: Diseases of the Liver, 6th ed. Schiff, L. and Schiff, E.R. (Eds.). New York: J.B. Lippincott Company, 1987.

PLATE XI

A. PRIMARY HEPATIC OSTEOSARCOMA

(Plate XI-A and figures 301-303 are from the same patient)

This cut surface of a primary hepatic osteosarcoma shows a large cystic cavity. The gritty surface is dense fibrosis with minute calcification. (Courtesy of Drs. Steve Romansky and C. Petrie, Fullerton, California.)



B. METASTATIC CARCINOMA

These multiple nodules of similar size have a hyperemic margin at the interface of normal liver tissue and the metastatic carcinoma (primary in the pancreas).

Figure 310
METASTATIC CARCINOMA
These multiple nodules of metastatic carcinoma (of pancreatic origin) show larger nodules with umbilication (retraction of the center) of the subcapsular area.

Figure 311
METASTATIC ADENOCARCINOMA
This metastatic adenocarcinoma in a noncirrhotic liver has liquefactive necrosis of the larger nodules of the fleshy, white tumor.

Figure 312
METASTATIC CARCINOMA
This metastatic carcinoma (oat cell from the lung) has a miliary spread with numerous small nodules diffusely spread throughout all lobes of the liver.

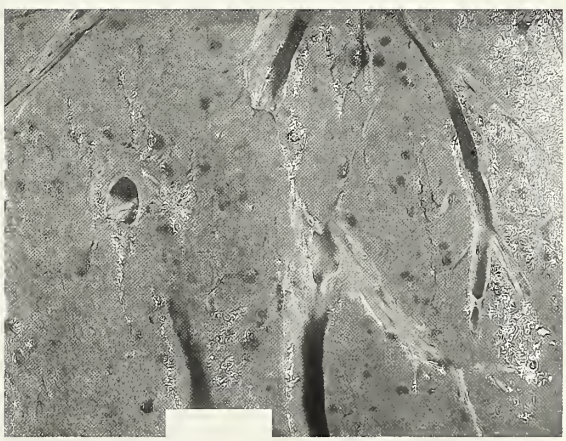


Figure 313
METASTATIC KAPOSI'S SARCOMA
This is a normal liver with metastatic Kaposi's sarcoma that appears as small, brown-black foci without much hemorrhage or necrosis.

The distribution of tumors within the liver is helpful in recognizing certain primary tumors (Table 15). Colonic adenocarcinoma is a common metastatic tumor and often produces a large single mass with numerous small satellites (fig. 311). Miliary spread of tumor is rare but occurs with prostatic adenocarcinoma (fig. 312). The cut surface of metastatic tumor may be glistening, even slimy, if from an adenocarcinoma, or granular and caseous if from a squamous carcinoma. Hemorrhagic metastatic tumors include choriocarcinoma, thyroid carcinoma, renal cell carcinoma, angiosarcoma, and melanoma. Kaposi's sarcoma is not as hemorrhagic as the previous tumors (fig. 313). Melanoma may be pigmented and either diffuse or mixed with diffuse and expanding forms. "Fish flesh" texture is common for tumors that are undifferentiated and cellular such as oat cell carcinoma, bronchogenic carcinoma, melanoma, non-Hodgkin's lymphoma, and some sarcomas. Necrosis is common in both adenocarcinoma and squamous carcinoma, especially if the nodules are large.

The microscopic features of metastatic tumors vary considerably. Some metastatic tumors have a distinctive appearance that resembles the primary site, but other tumors incite a local reaction. A fibrous reaction to the metastatic tumor is common for the breast and pancreas (figs. 314-316). Some neoplasms fail to stimulate a parenchymal response and the

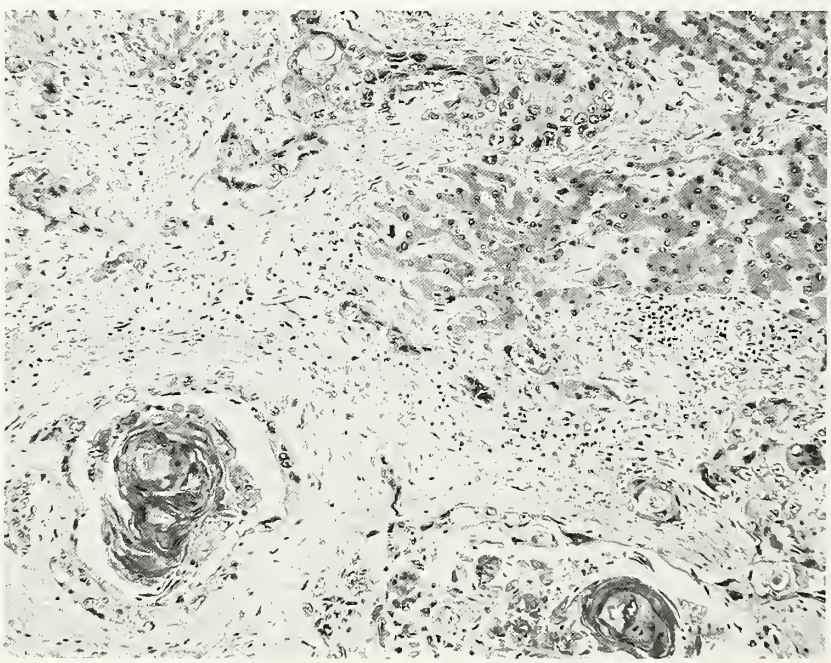


Figure 314
METASTATIC SQUAMOUS CARCINOMA
As illustrated in this figure, metastatic squamous carcinoma may have a fibrous reaction separating the tumor from the hepatic parenchyma. X117.

Figure 315
METASTATIC MELANOMA
This metastatic melanoma has a brown cytoplasmic pigment within the large pleomorphic cells, and in this figure, has a fibrous band separating the tumor from the adjacent liver. X45.

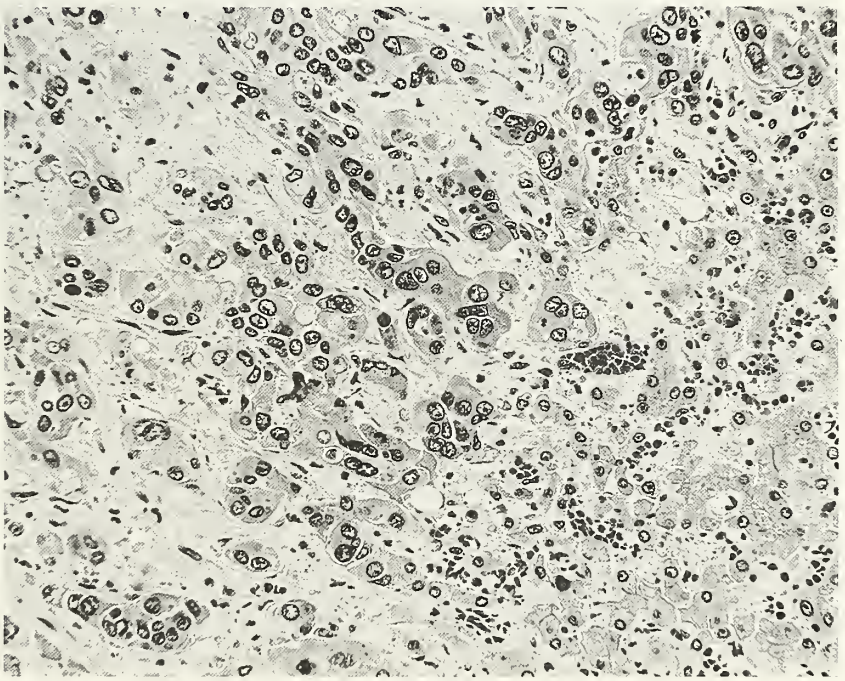


Figure 316
METASTATIC PANCREATIC ADENOCARCINOMA
The metastatic pancreatic adenocarcinoma in this field has collagen and bland stroma around the chains of eosinophilic cells. Although a trabecular pattern may be noted at a low magnification, a sinusoidal lining cell is absent, and no bile production is present. X235.

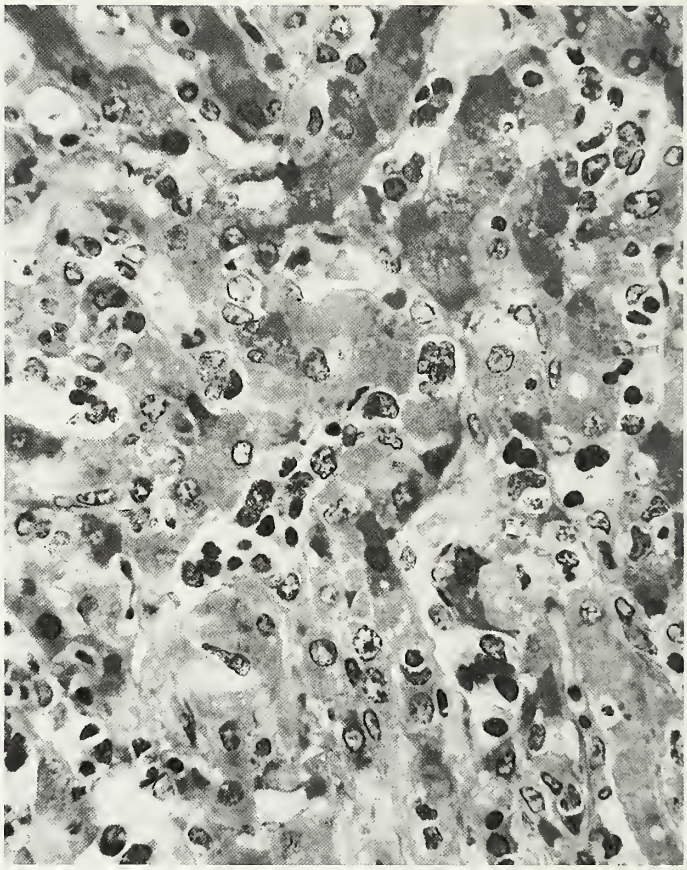


Figure 317
METASTATIC OAT CELL CARCINOMA
This metastatic oat cell carcinoma lacks cohesiveness, infiltrates through the sinusoids, and is adjacent to individual hepatocytes. X575.

tumor grows in the sinusoids without a reaction (fig. 317). Some metastatic tumors may form a trabecular-like pattern resembling hepatocellular carcinoma, but at a higher magnification, the sinusoidal lining pattern is minimal or absent, and the individual cells do not form any acini. Melanoma may be difficult to distinguish in small samples because, like hepatocellular carcinoma, the tumor cells have large nuclei with prominent nucleoli. Special stains for melanin are advised (fig. 318). Sinusoidal growth is typical for undifferentiated tumors, including oat cell carcinoma, (small cell carcinoma) and may resemble hepatocellular carcinoma (fig. 317). Undifferentiated tumors usually grow in the sinusoids and may not form large masses.

Differential Diagnosis. Adenocarcinoma in the liver usually resembles the known primary site, but the presence of a tumor with an unknown primary is a common problem without clear-cut solutions. Cholangiocarcinoma has histologic

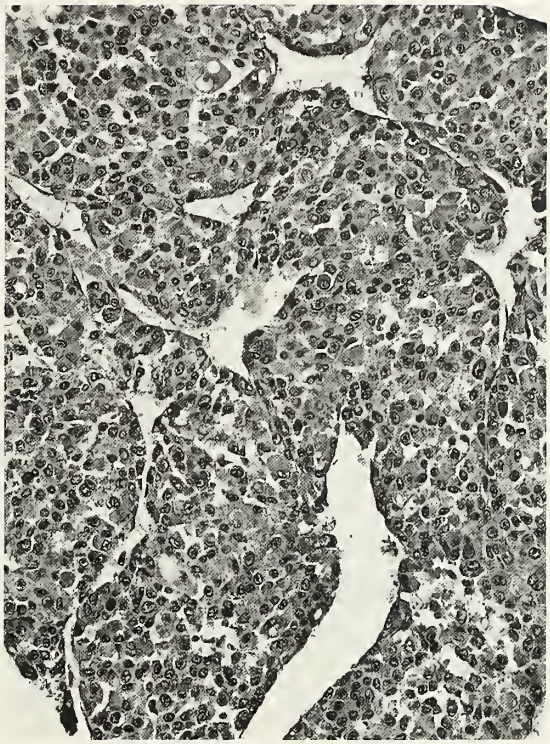


Figure 318
METASTATIC MELANOMA
This metastatic melanoma is from a 65 year old woman who had no known primary and had resection of a large left lobe tumor. The eye was enucleated 4 years before for glaucoma and may have been the unproven source of melanoma. X620. (Courtesy of Dr. Malcolm Forsberg, Los Angeles, California.)

features similar to numerous metastatic adenocarcinomas. Hepatocellular carcinoma may mimic renal cell carcinoma, adrenal carcinoma, and melanoma because all may have trabecular growth and endothelial lining cells. Special technics such as immunoperoxidase have not produced uniform results. Accurate classification of metastatic and primary hepatic tumors is not yet reliably accomplished by light microscopy in all tumors, and special stains assist in some additional tumors. Alpha-fetoprotein, which is often identified in hepatocellular carcinoma (in serum primarily, but also often by immunohistochemical means), may occur in very high levels in gastric adenocarcinomas as well as germ cell neoplasms.

Prognosis. Resection of selected hepatic metastasis may be beneficial if there are less than three isolated lesions equal to or smaller than 5 cm in diameter (Malt).

OTHER METASTATIC TUMORS
(LYMPHOMA, HODGKIN'S DISEASE, AND OTHER MONONUCLEAR PHAGOCYTE SYSTEM TUMORS)

Lymphoma metastatic to the liver is relatively common and occurs in 20 percent of patients with non-Hodgkin's lymphoma at diagnosis, and approximately 55 percent at autopsy (Roth et al.). The typical hepatic involvement is monotonous lymphocytes in the portal area with separation of the normal portal components by the lymphocytic tumor. The bile duct, arteriole, and portal vein seem to float in the sea of lymphocytes, which do not appear oriented to any specific structure. Individual cells infiltrate the sinusoids later in the growth of the lymphoma. An epithelioid histiocytic reaction occurs in the liver of patients with non-Hodgkin's lymphoma and does not indicate lymphomatous involvement (Jaffe). Adult T cell lymphoma commonly involves the liver (50 percent of the patients) and is identified by sinusoidal infiltration as well as prominent portal lymphocytic collections. The diagnosis of Hodgkin's disease within the liver should only be made if diagnostic Reed-Sternberg cells are identified within the liver (Jaffe). Nonspecific inflammatory infiltrates are seen in approximately 50 percent of the liver biopsies from patients with Hodgkin's disease and only 5 percent have the diagnostic features of Hodgkin's disease. Hairy cell leukemia typically infiltrates the sinusoids and portal areas with a monotonous, large, lymphocytic-like cell (fig. 319).

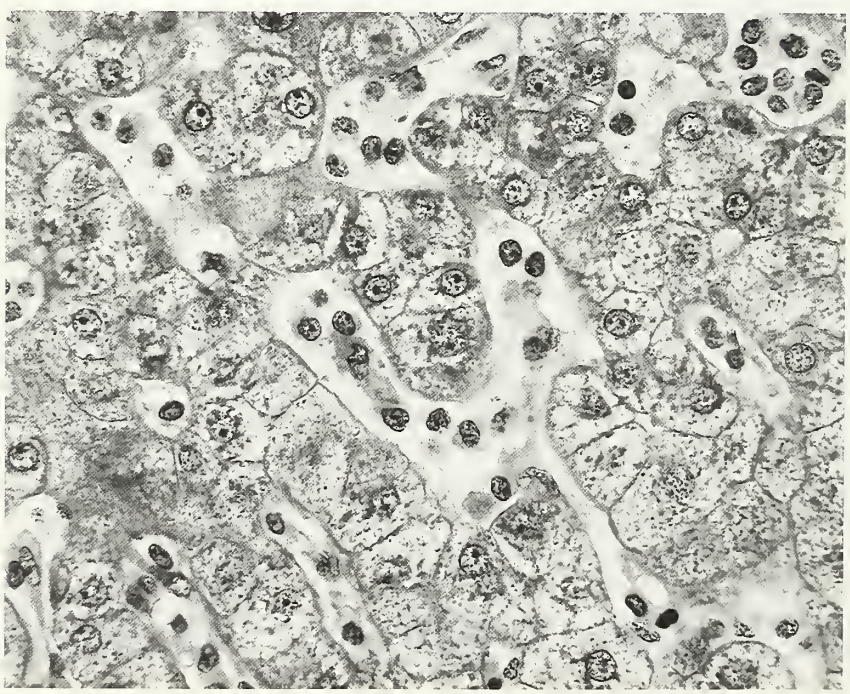


Figure 319
HAIRY CELL LEUKEMIA
This hairy cell leukemia is characterized by diffuse infiltration in the sinusoids by uniform small cells, often with cytoplasmic projections that may be noted with good processing technics and thin sections. X1170. (Courtesy of Dr. Peter Rosen, Los Angeles, California.)

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